

Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours

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Abstract

Although recent epidemiological evidence indicates that the prevalence of non-functioning gastroenteropancreatic (GEP) neuroendocrine tumours (NETs) is rising, a significant number of GEP-NETs still present with symptoms related to the secretion of biologically active substances leading to the development of distinct clinical syndromes. In the past, these syndromes were associated with substantial morbidity and mortality due to the lack of specific therapies; however, since the introduction of long-acting somatostatin analogues and medications such as proton pump inhibitors, their control has been greatly improved. As a result, nowadays, the main cause of morbidity and mortality in GEP-NETs is mostly directly related to tumour growth and the extent of metastatic disease. However, in some patients with functioning tumours and extensive disease, control of the secretory syndrome still remains problematic, necessitating the employment of several cytoreductive techniques, which may not always be sufficient. Recently, new agents directed against tumour growth, or exerting increased binding activity to receptors expressed in these tumours, or interfering with the synthetic pathway of some of the compounds secreted by these tumours, have been developed. Since there are no specific guidelines addressing the totality of the management of the secretory syndromes related to GEP-NETs, this review aims at critically analysing the medical management of previously recognised secretory syndromes; it also addresses areas of uncertainty, assesses the newer therapeutic developments and also addresses recently described but poorly characterised secretory syndromes related to GEP-NETs.

Key Words

- ▶ neuroendocrine tumours
- ▶ secretory syndrome
- ▶ carcinoid syndrome
- ▶ insulinoma
- ▶ VIPoma
- ▶ glucagonoma
- ▶ ectopic hormonal secretion

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Introduction

Gastroenteropancreatic (GEP) neuroendocrine tumours (NETs) are considered to be relatively rare, with an estimated incidence of 3–5 cases per 100,000 inhabitants; however, recent data indicate that their prevalence is increasing following the introduction of newer more sensitive biochemical and imaging modalities (Modlin *et al.* 2008, Huguet *et al.* 2015). In the past GEP-NETs came to medical attention due to their ability to secrete biologically active substances leading to the development of characteristic clinical syndromes (functioning tumours). Nowadays the majority of GEP-NETs do not cause secretory syndromes and present with metastases or symptoms of mass effect (non-functioning tumours) (Kaltsas *et al.* 2004). Neuroendocrine tumours are considered to originate from multipotent cells scattered throughout the gastrointestinal (GI) system that belong to the diffuse endocrine system, and have the ability to synthesise and secrete peptides and amines, a number of which can be bioactive (Kaltsas *et al.* 2004, Modlin *et al.* 2008). Traditionally, secretory syndromes were attributed to tumours originating from the pancreas (pancreatic NETs, pNETs) and the so-called midgut ('carcinoid') tumours, the majority of which were derived from the ileum (Table 1). More recently, it has become apparent that some of these tumours are capable of secreting substances that are considered to originate from other tissues, making their diagnosis and identification difficult. Furthermore, NETs that were apparently considered to be initially non-functioning may acquire (during the course of the disease) the ability to secrete specific compounds

and become functioning, whereas functioning tumours may alter their secretory profile by secreting a different compound (Tomassetti *et al.* 2001, Kaltsas *et al.* 2004, Crona *et al.* 2016). Very recently, a number of newly characterised secretory syndromes that are not previously recognised have been identified, highlighting the need of increased awareness of these functioning NETs and potential alterations of their secretory component in order to identify them and provide appropriate treatment.

In the past, functioning GEP-NETs were associated with increased morbidity and mortality due to the lack of any specific treatment. However, following the demonstration that the majority of GEP-NETs express somatostatin receptors (SSTRs) on their cell surface, and the introduction of long-acting somatostatin analogues (SSAs) that exhibit an overall inhibitory secretory effect in tumours bearing such receptors, significant symptomatic control was obtained in many of the functioning NETs (Kvols *et al.* 1985, Kaltsas *et al.* 2004, Modlin *et al.* 2010). Indeed, patients with a number of secretory syndromes related to GEP-NETs obtained substantial symptomatic and biochemical responses to these agents, although their effect on tumour growth was not as prominent (Modlin *et al.* 2010). In addition, proton pump inhibitors (PPIs) have also proven to be efficacious in controlling the secretory syndrome related to excessive gastrin secretion (Ito *et al.* 2013). The introduction of these medications along with the use of various other drugs has resulted in a significant reduction in morbidity and mortality related to functioning GEP-NETs. In addition, the development of more potent SSAs and compounds that inhibit the synthetic pathway of specific bioactive

Table 1 Classification of GEP-NETs according to their secretory component.

GEP-NET	Syndrome	Incidence (new/100,000 year)	Secretory component
Carcinoid tumours	Carcinoid syndrome	2–3	Serotonin, tachykinins
Gastrinoma	Zollinger–Ellison syndrome (ZES)	0.5–1.0	Gastrin
Insulinoma	Endogenous hyperinsulinism	0.5–1.0	Insulin
VIPoma	Verner–Morrison syndrome, WDHA	0.05–0.1	VIP
Glucagonoma	Glucagonoma	0.01–0.05	Glucagon
Somatostatinoma	Somatostatinoma	<0.01	Somatostatin
ACTHoma	ACTH	<0.05	ACTH
GHRHoma	GHRH	Unknown	GHRH
pNET causing carcinoid syndrome	Carcinoid syndrome	Unknown	Serotonin, tachykinins
pNET causing hypercalcaemia	PTHrPoma	<0.1	PTHrP
Rare pNETs	LH, rennin, GLP-1, IGF-2, erythropoietin, CCK, enteroglucagon	1–5 cases	Various hormones

ACTH, adrenocorticotrophin hormone; CCK, cholecystokinin; GHRH, growth hormone-releasing factor; GLP-1, glucagon-like peptide 1; IGF-2, insulin growth factor 2; LH, luteinising hormone; PTHrP, parathyroid hormone-releasing peptide; VIP, vasointestinal peptide; WDHA, watery diarrhoea hypokalaemia achlorhydria.

substances has further expanded our therapeutic options. However, a number of secretory syndromes related to GEP-NETs such as the carcinoid syndrome (CS), with or without an associated carcinoid crisis, and malignant insulinomas, along with malignant pheochromocytomas/paragangliomas, still comprise a significant cause of mortality, as the control of secretory component may still not be possible in many cases.

Rationale for treatment of functioning GEP-NETs with SSAs

As early as the 1980s, it was demonstrated that native somatostatin (SS-14) could ameliorate many of the symptoms of the CS (Thulin *et al.* 1978). Because native SS has a relatively short half-life, synthetic compounds mimicking its action but with significantly longer half-lives have been developed. Octreotide was the first synthetic SSA exhibiting high affinity for SSTRs type 2 and 5 (SSTR 2,5) to have been introduced into clinical practice (Bauer *et al.* 1982). Since the majority of GEP-NETs express SSTRs on their surface, it became apparent that they represent ideal targets for these compounds (Kvols *et al.* 1985, Kaltsas *et al.* 2004). Initially, subcutaneous (s.c.) injection of octreotide was shown to control symptoms in patients with functioning NETs (Wood *et al.* 1985) and prevent the development of carcinoid crisis in patients with CS undergoing invasive procedures or surgery (Kvols *et al.* 1985). The development of a depot formulation of octreotide LAR ('long-acting repeatable') (Novartis), administered at doses of 30 mg at monthly intervals, substantially reduced the need for daily octreotide injections (Rubin *et al.* 1999). However, the latter can still be used as 'top-up' doses in cases of symptom breakthrough, due to either resistance or waning of the octreotide LAR effect over the month, fluctuations of hormonal levels secreted by the tumour or tumour progression (Rubin *et al.* 1999, Kaltsas *et al.* 2004, Modlin *et al.* 2010). A number of other octapeptide analogues with similar actions to octreotide have also been synthesised, the most extensively used being lanreotide; this is also available in a long-acting formulation, the most convenient being lanreotide autogel (Ipsen). Long-acting SSAs (octreotide and lanreotide) are the best available option for symptom relief from secretory tumours bearing SSTRs on their surface, irrespective of the secretory components being either amines or peptides (Modlin *et al.* 2010). Furthermore, new synthetic SSAs with affinity for additional SSTRs have been synthesised in an attempt to increase the efficacy of these compounds (Table 2). It has previously been noticed that an escape

Table 2 Native somatostatin and somatostatin receptor subtype-binding affinity of currently available long-acting somatostatin analogues.

Compound	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Native somatostatin and somatostatin analogue receptor subtype affinity (IC ₅₀ , nM)					
Somatostatin-14	2.26	0.23	1.43	1.77	0.88
Somatostatin-28	1.85	0.31	1.3	–	0.4
Octreotide	1140	0.56	34	7030	7
Lanreotide	2330	0.75	107	2100	5.2
Pasireotide	9.3	1	1.5	>100	0.16

SSTR, somatostatin receptor.

phenomenon regarding symptomatic control may develop in patients treated with SSAs over times ranging from a few months to many years (Hofland & Lamberts 2003). Although this has been merely attributed to desensitisation of tumour-related hormonal secretion by SSAs, it is most commonly encountered following tumour progression and an increase in the secretory component leading to a reduction in the efficacy of SSAs (Hofland & Lamberts 2003, Kaltsas *et al.* 2004, Strosberg *et al.* 2013).

Symptomatic treatment of CS

The classical (typical) CS is usually characterised by cutaneous flushing, gut hypermobility with diarrhoea and bronchospasm, mostly encountered in patients with small intestinal carcinoids and hepatic metastases (Tomassetti *et al.* 2001, Kaltsas *et al.* 2004). A less common atypical CS may be found with tumours originating from the former foregut, mainly lung carcinoids with liver metastases, and is due to the release of both histamine and serotonin (Tomassetti *et al.* 2001, Papadogias *et al.* 2007). If CS remains untreated over a prolonged period, it may lead to a number of nutritional deficiencies, the development of carcinoid heart disease (CHD) and other fibrotic changes involving the mesentery (Kaltsas *et al.* 2004, Grozinsky-Glasberg *et al.* 2015).

Specific treatment directed against the symptoms of CS

Before the introduction of SSAs, several therapies aiming at ameliorating symptoms rather than specifically reducing serotonin production were used (Kaltsas *et al.* 2004, Modlin *et al.* 2008). Subsequent studies using 150 µg of s.c. octreotide three times a day in patients with CS showed an almost 88% response in flushing and diarrhoea that was accompanied with a greater than 50% decrease in 5-hydroxyindoleacetic acid (5-HIAA) levels in 72% of the treated patients (Kvols *et al.* 1986, Modlin *et al.*

2010). Subsequent studies using s.c. octreotide at doses ranging from 50 to 1000 µg, but occasionally up to 3 mg, 2–3 times per day, showed that significant symptomatic improvement of CS was obtained. An analysis of 10 studies that evaluated more than 300 patients with CS treated with s.c. octreotide, with doses ranging between 150 and 3000 µg (median dose 450 µg), showed 70% control of both flushing and diarrhoea (Kvols *et al.* 1986, Vinik & Moattari 1989, Anthony *et al.* 1993, Janson & Oberg 1993, Saltz *et al.* 1993, Arnold *et al.* 1996, di Bartolomeo *et al.* 1996, Rubin *et al.* 1999, O'Toole *et al.* 2000, Aparicio *et al.* 2001). A randomised study comparing daily s.c. injections of short-acting octreotide to octreotide LAR at various doses every 4 weeks demonstrated an at least equivalent symptomatic control (Rubin *et al.* 1999). Similar to octreotide LAR, long-acting lanreotide exhibits equal affinity for SSTR type 2 and 5 (Modlin *et al.* 2010). A pooled data analysis of symptomatic responses (diarrhoea and flushing) to octreotide LAR ($n=122$ patients) and long-acting lanreotide ($n=185$ patients) showed a mean symptomatic response of 74.2% (range 61.9–92.8%) and 67.5% (range 40–100%), respectively (Modlin *et al.* 2010). In addition, these agents have the advantage of being associated with a very low side-effect profile and are thus well tolerated (Kaltsas *et al.* 2004, Modlin *et al.* 2010, Strosberg *et al.* 2013). However, potential side effects may occasionally develop and need to be considered, as many patients are treated with these compounds for a prolonged period (Table 3).

When symptom control is inadequate, top-up doses of 50–100 µg (up to 1000 µg) of short-acting octreotide s.c. can be given or alternatively the frequency or dose of long-acting SSA administration can be increased (Rubin *et al.* 1999, Strosberg *et al.* 2014). In an initial prospective study, 28 patients with CS with disease progression during therapy with octreotide LAR 30 mg every 28 days exhibited complete and partial control of symptoms after octreotide LAR 30 mg administration every 21 days in 40 and 60% of the cases, respectively; circulating biomarkers were significantly decreased in 30% (Ferolla *et al.* 2012).

Significantly higher doses, particularly of octreotide LAR ranging from 40 to 90 mg (Anthony *et al.* 2011, Fiebrich *et al.* 2010), have been used in clinical practice in patients with suboptimal symptomatic control of CS or tumour growth while being on the approved maximum label dose of 30 mg every 4 weeks (Rubin *et al.* 1999). An analysis of a single-centre study evaluating patients treated with 40 mg octreotide LAR every 4 weeks, octreotide LAR 60 mg every 4 weeks and octreotide LAR 30 mg every 3 weeks showed an overall improvement of diarrhoea in 34 (63%) and flushing in 28 patients (56%) over conventional dosing (Strosberg *et al.* 2013). A subsequent multicentre study of 239 patients who had received a series of escalating doses of octreotide LAR also showed a similar beneficial effect in symptom control (Strosberg *et al.* 2014). However, these studies were hampered by their retrospective nature and the lack of quantitative measurements of changes in flushing and diarrhoea, as all information was collected after reviewing patients' charts (Strosberg *et al.* 2014). Nevertheless, a significant finding from all these studies was that there was no increased toxicity with doses of octreotide even as high as 120 mg/month (Anthony *et al.* 2011, Strosberg *et al.* 2014, Broder *et al.* 2015).

Although octreotide and lanreotide target mainly SSTRs 2 and 5, GEP-NETs express multiple subtypes of SSTRs on their surface (Bruns *et al.* 1994). Pasireotide is a multireceptor targeting SSA with high affinity to all SSTRs except SSTR type 4 (Bruns *et al.* 2002). It was hypothesised that pasireotide might ameliorate the symptoms of CS in patients inadequately controlled with 30 mg octreotide LAR. In a phase II study, 45 patients with symptoms refractory to 30 mg octreotide LAR, in whom specific criteria to define inadequate control of bowel movements (≥ 4 per day) or flushing episodes (≥ 2 per day) as well as response to treatment were predefined, pasireotide was administered at increasing doses (Kvols *et al.* 2012). Pasireotide at doses 600–900 µg twice daily effectively controlled the symptoms of diarrhoea and flushing in 27% of the patients, with the most common side effects being nausea, abdominal pain, weight loss

Table 3 Side effects attributed to long-acting somatostatin analogues (data from Van der Lely *et al.* 1997, Hovind *et al.* 2010)

Frequent side effects (>10% of patients)	Headaches, fatigue, gastrointestinal symptoms (abdominal pain, cramps, nausea/vomiting, diarrhoea/constipation), biliary tree abnormalities (sludge without stones, gallstones, bile duct dilatation), arthropathy and back pain, insulin secretion abnormalities (hyperglycaemia 10%, hypoglycaemia 2%)
Common side effects (>1% of patients)	Slow heart rate (cardiac conduction changes), skin reactions (pruritus), hyperbilirubinaemia, hypothyroidism, dizziness, dyspnoea
Rare side effects	Anaphylactic reactions, pancreatitis, hepatitis
Extremely rare side effects	Alopecia, QT abnormalities

and hyperglycaemia (Kvols *et al.* 2012). A subsequent phase III study that evaluated the ability of pasireotide LAR 60mg and octreotide LAR 40mg in controlling the symptoms of CS in patients refractory to currently labelled maximum doses of SSAs demonstrated that both agents showed similar symptomatic control (20.9% vs 26.9%, respectively), although pasireotide was associated with a higher incidence of side effects, particularly hyperglycaemia (28.3% vs 5.3%, respectively) (Wolin *et al.* 2015). From the data derived from this prospective study, the above-labelled octreotide LAR doses (at least octreotide LAR 40mg) are expected to induce an approximately 30% improvement in refractory to conventional doses of SSA symptoms rather than the previously described higher response rates (Strosberg *et al.* 2013, 2014).

Another agent that has been shown to have activity in controlling the symptoms in patients with CS is interferon- α (Oberge 2000). Initially, human and subsequently recombinant interferon- α were used at doses of 3–9MU daily or on alternate days (median dose 5MU titrated individually according to sex, weight and age) (Oberge 2000). Although interferon- α controls the symptoms of CS in 40–70% of the patients, its use is associated with substantial adverse effects including fever, fatigue, anorexia and weight loss, autoimmune diseases and myelosuppression and is considered as a second-line treatment (Kaltsas *et al.* 2004). Currently, pegylated interferon- α has been introduced that is expected to induce fewer side effects. Considering that interferon- α produces the upregulation of SSTRs in *in vitro* studies, and the combination with SSAs shows a stronger *in vivo* anti-proliferative effect than either drug alone, it was suggested that their combination might exhibit a synergistic effect (Hofland *et al.* 1999). This concept was addressed in two prospective studies. In one, lanreotide and interferon- α were shown to exert a superior symptomatic control compared with each compound alone, albeit with more side effects (Faiss *et al.* 2003). However, there was no difference in respect to symptom control when octreotide alone was compared with the combination of octreotide and interferon- α (Arnold *et al.* 2005). On the basis of these findings, this combination has not found wide application in clinical practice in terms of symptomatic control, although it has been suggested that lower than previously used doses of interferon- α in combination with SSA may still merit investigation in properly designed randomised trials (Fazio *et al.* 2007).

For refractory cases that cannot be controlled with long-acting SS analogues (either octreotide or lanreotide), a number of phase I/II and a recent phase III studies have

shown that telotristat etiprate, an orally administered serotonin synthesis inhibitor, may have an additional effect (Kulke *et al.* 2014, Pavel *et al.* 2015). Telotristat etiprate is a small molecule that does not cross the blood–brain barrier and thus has no central nervous system side effects, as it does not deplete serotonin levels in the brain (Pavel *et al.* 2015). Its mode of action is by inhibiting tryptophan hydroxylase, the rate-limiting enzyme in the conversion of tryptophan to serotonin (Kulke *et al.* 2014). In an initial randomised prospective study designed to assess the safety and efficacy of telotristat in patients with predefined criteria of inadequate symptom control of CS with the highest labelled dose of octreotide LAR, 18 patients were assigned to increasing doses of telotristat etiprate (150, 250, 350, 500mg three times daily) and were compared with controls (Kulke *et al.* 2014). Approximately, 30% of the patients experienced a $\geq 30\%$ reduction in bowel movement frequency for ≥ 2 weeks, whereas 56% reported adequate relief of at least 1 of the 4 weeks of treatment; adverse effects were generally mild and mainly GI in nature (Kulke *et al.* 2014). In a subsequent open label with dose escalation over 12 weeks in a prospective study of responses to telotristat in patients refractory to SSAs, 14 patients were evaluated while on concomitant SSA treatment (Pavel *et al.* 2015). All patients experienced reductions in the number of bowel movements per day (mean decrease, 43.5%) associated with additional 5-HIAA level reductions; in addition, stool form and flushing episodes were also improved notwithstanding that the latter are not predominantly serotonin mediated (Pavel *et al.* 2015). It was thus suggested that telotristat etiprate could offer a further therapeutic option in patients refractory to SSAs, particularly as it is associated with minimal side effects. While these improvements may not seem dramatic, it may also be that the decrease in serotonin synthesis might reduce the onset of peritoneal and especially cardiac valvular fibrosis, which would be valuable therapeutic benefits. Irrespective of advances in currently available drugs, treatment with intravenous octreotide infusion in patients with refractory CS may still be tried, at least temporarily, to provide symptomatic control until treatment debulking options could also be considered.

Non-specific treatment and treatment directed against the sequel of CS

As diarrhoea and flushing can be induced by specific precipitants, lifestyle adjustments in patients with CS may need to be considered and implemented. Patients

with diarrhoea should avoid known precipitants such as strenuous exercise, consumption of spicy foods and excessive alcohol intake. Loperamide and codeine phosphate can be of additional help in refractory cases of diarrhoea; loperamide in particular can be used in cases of breakthrough diarrhoea in doses up to 16 mg daily (Kaltsas *et al.* 2004). Diarrhoea can also result following the resection of the primary tumour and nearby normal bowel at the terminal ileum, secondary to bile acid loss and/or bacterial overgrowth from a blind enteric loop, which may cause deconjugation of bile acids (Kaltsas *et al.* 2004). Patients with diarrhoea secondary to bile acid deconjugation respond to treatment with cholyseramine or related agents, whereas antibiotics should be administered in cases of bacterial overgrowth (Tomassetti *et al.* 2001, Kaltsas *et al.* 2004). The flush of typical CS is usually triggered by alcohol or tyramine-containing foods, chocolate and bananas. As serotonin is not the main secretagogue, histamine-2 receptor antagonists are also of proven value in this situation (Kaltsas *et al.* 2004, Papadogias *et al.* 2007). It should also be remembered that major pancreatic resection, in cases of pancreatic carcinoids, may lead to loss of pancreatic exocrine function, and replacement with enzymes such as *Creon* with meals may be beneficial. These supplements may also be used to treat SSA-induced steatorrhoea. This is particularly important as a recent study using a validated questionnaire revealed that a significant number of patients with NETs who are on treatment with SSAs are at high risk of malnutrition (Qureshi *et al.* 2016). Uncontrolled diarrhoea may be debilitating causing dehydration, electrolyte abnormalities, vitamin deficits and hypoproteinaemia (Kaltsas *et al.* 2004). In the presence of severe CS, the essential amino acid tryptophan is converted to serotonin, leaving inadequate amounts of tryptophan for conversion to niacin and proteins (Bouma *et al.* 2015). Niacin deficiency can lead to pellagra, with the development of dermatitis, diarrhoea and dementia (Bouma *et al.* 2015). Other symptoms such as aggression, ataxia, insomnia, confusion and cardiomyopathy may also be present. Diagnosis can be confirmed after rapid improvements in the symptoms in patients using high doses of niacin (50–500 mg/day) or niacin-enriched food (Kaltsas *et al.* 2004, Bouma *et al.* 2015). A combination of vitamin B supplements should be administered to patients with severe diarrhoea and any suspicion of pellagra, and/or with high 5-HIAA output. In addition, deficiencies of other fat-soluble vitamins, which may occasionally follow treatment with SSAs, should be sought and adequately substituted (Fiebrich *et al.* 2010).

CHD develops as a result of the fibrotic effect of the excessive amounts of serotonin on heart valvular leaflets. Patients with 5-HIAA levels $\geq 300 \mu\text{mol}/24 \text{h}$ and ≥ 3 episodes of flushing per day are at increased risk of developing CHD (Bhattacharyya *et al.* 2011, Grozinsky-Glasberg *et al.* 2015). In case of clinically significant CHD, cardiothoracic surgical evaluation and possible surgical valvular replacement may be required before any major intervention or surgery (Connolly *et al.* 2001, Grozinsky-Glasberg *et al.* 2015). It is possible that the early use of telotristat etiprate may delay or avoid such problems.

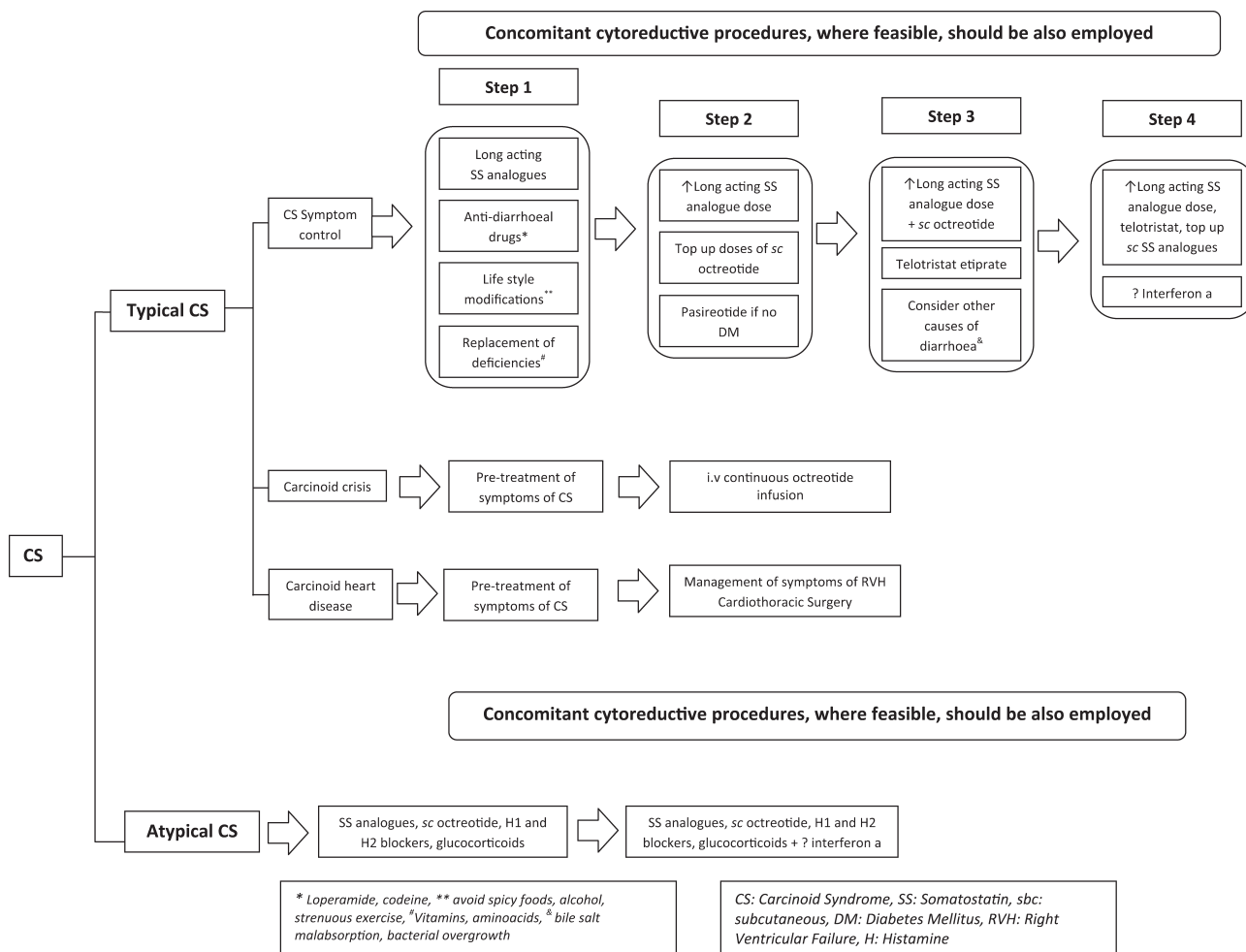
Carcinoid crisis

Patients with CS are at risk for developing a carcinoid crisis, characterised by excessive flushing, alterations in thermoregulation, bronchospasm and haemodynamic instability, mainly in the form of hypotension (Condrón *et al.* 2016). The crisis may occur following diagnostic or therapeutic procedures, induction of anaesthesia and/or as a result of tumour manipulation (Plöckinger *et al.* 2004). Intravenous continuous octreotide infusions administered 12 h before any high-risk procedure at a starting dose of 50–100 $\mu\text{g}/\text{h}$ (doses up to 3 mg have been used) with dose escalation until symptom control is obtained (mean dose 100–200 $\mu\text{g}/\text{h}$) is the treatment of choice (Ramage *et al.* 2012). Patients pre-treated with SSAs may require even higher doses and treatment should be continued at least 48 h after the end of the procedure, as late-onset events have been described (Ramage *et al.* 2012). However, a recent analysis of 127 patients who underwent surgical procedures with concomitant continuous octreotide infusion demonstrated that a carcinoid crisis may still develop, particularly in patients with hepatic metastases and symptoms of CS, although neither was required for a crisis to occur (Condrón *et al.* 2016). Combination treatment with H1 and H2 receptor blockers may also be administered, along with glucocorticoids, since histamine release and its peripheral actions are not completely blocked by SS analogues (Kaltsas *et al.* 2004, Plöckinger *et al.* 2004) (Fig. 1).

Symptomatic treatment of functioning pNETs

Insulinomas

The great majority of insulinomas (>90%) are identified early and can be surgically cured as they are non-metastatic at presentation (de Herder *et al.* 2011). Such patients should

**Figure 1**

A step-by-step algorithm of management of carcinoid syndrome, carcinoid crisis and sequelae.

preferably be submitted to surgery without delay and often without prior systemic treatment to counteract excessive insulin secretion, as this can be usually controlled with frequent small volume carbohydrate-enriched meals (Kaltsas *et al.* 2004, de Herder *et al.* 2011). In insulinoma patients with significant pre-surgical hypoglycaemia, additional symptomatic or systemic therapy may be required. The control of insulin hypersecretion may also be difficult in cases of metastatic tumours not amenable to surgery or other cytoreductive modalities. In such cases, patients may require continuous nocturnal feeding via a nasogastric tube, drugs to lower insulin hypersecretion or even continuous intravenous glucose administration (de Herder *et al.* 2011, Bernard *et al.* 2013). At times of intractable hypoglycaemia, high glucose concentration administration along with intra-muscular glucagon and potassium replacement may be required as a rescue procedure. Diazoxide, which suppresses insulin secretion from insulinoma cells via an

effect on the ATP-sensitive potassium (KATP) channels, has been extensively used at doses 50–300mg/day (max dose up to 600mg/day) (Kaltsas *et al.* 2004, de Herder *et al.* 2011). This drug has several side effects including GI complaints and oedema, renal impairment and hirsutism, and is usually combined with thiazide diuretics to lower total body potassium and counteract oedema and sodium retention (Kaltsas *et al.* 2004, de Herder *et al.* 2011). In addition, there is little information regarding its long-term tolerability and its effect in metastatic insulinomas (Bernard *et al.* 2013). Although there have been some reports of a hypoglycaemic effect of β -blockers, calcium blockers and phenytoin, these agents have not been shown to be markedly efficacious in clinical practice (Kaltsas *et al.* 2004, de Herder *et al.* 2011). Treatment with long-acting SSAs has been used in patients with insulinomas, but these drugs may worsen hypoglycaemia in approximately 50% of the cases when tumours lack SSTR2 and 5 expression as

glucagon secretion is also inhibited; treatment should be initiated only in patients with positive SSTR scintigraphy (SRS) and after the effect of a test dose of octreotide has been evaluated, preferably at an in-patient setting (Bruns *et al.* 2002, Vezzosi *et al.* 2005). However, octreotide was shown to be effective in controlling hypoglycaemia in more than 50% of the patients with insulinomas and a positive SRS, and in a few with negative scans, whereas there was no relation between treatment efficacy and the expression of SSTR5 (Vezzosi *et al.* 2005). Other studies have also demonstrated a similar ability of SS analogues in controlling cases of hypoglycaemia (Baldelli *et al.* 2014). As opposed to benign insulinomas, malignant insulinomas often lack GLP-1 receptors but express SSTR2 receptors in a higher proportion compared with benign lesions, and thus paradoxically respond better to SS analogues (Wild *et al.* 2011). Furthermore, as pasireotide commonly induces hyperglycaemia, it can also be used in cases of hypoglycaemia not responding to first-generation SS analogues. To date, there is (to our knowledge) only a single case report supporting the beneficial effect of pasireotide in a case of hypoglycaemia refractory to other treatments due to a malignant insulinoma (Tirosch *et al.* 2016).

In recent years, the mTOR inhibitor everolimus has been shown to exert a specific hyperglycaemic effect and counteract refractory hypoglycaemia in cases of metastatic insulinomas (Kulke *et al.* 2009, de Herder *et al.* 2011). The mTOR pathway plays a significant role in pNET progression and also in glucose homeostasis, enhancing insulin secretion and increased glucose utilisation (Bernard *et al.* 2013). In a number of phase II/III trials with several mTOR inhibitors, hyperglycaemia has emerged as a common side effect suggesting that this is probably a class effect of these drugs (Kulke *et al.* 2009, Bernard *et al.* 2013). Several hypotheses have been put forward to explain their hyperglycaemic effect including a decrease in insulin production and release and/or an increase in peripheral insulin resistance (Bernard *et al.* 2013), but probably decreased insulin release is the predominant therapeutic effect (Korevaar *et al.* 2014). Everolimus was shown to control refractory hypoglycaemia in four patients with metastatic insulinomas leading to discontinuation of diazoxide and glucose infusions (Kulke *et al.* 2009). Subsequently, further, patients showing a similar effect have been described, while in a multicentre retrospective study including 12 heavily pre-treated patients with metastatic insulinomas, introduction of everolimus was associated with a median period of normoglycaemia of 6.5 months irrespective of changes in tumour load (Bernard *et al.* 2013). In this particular study, everolimus appeared

to be superior to any other treatments counteracting hyperinsulinaemia, and was mostly given at doses 10mg/daily; there is, however, evidence that everolimus might still exert a hyperglycaemic effect if given at 5mg/daily or even on alternate days (Baldelli *et al.* 2014, Baratelli *et al.* 2014). In cases of refractory hypoglycaemia from insulinomas not amenable to any cytoreductive techniques, treatment with combination of all these medication may be necessary.

Gastrinoma and the Zollinger–Ellison syndrome

Zollinger–Ellison syndrome (ZES) occurs as a result of hypersecretion of gastrin, mostly from a GEP-NET of the duodenum or pancreas, although other sources such as thymic carcinoids have been described (Somasundaram *et al.* 2013). These tumours occur either sporadically or in the context of multiple endocrine neoplasia type 1 (MEN 1) in approximately 25–30% of the cases (Kaltsas *et al.* 2004, Jensen *et al.* 2012). The syndrome should also be suspected in patients with peptic ulcer disease resistant to treatment with PPIs and concomitant diarrhoea, and in the presence of hyperplastic gastric folds – ‘rugular hypertrophy’ (Kaltsas *et al.* 2004, Ito *et al.* 2013). As with other functioning NETs, the therapeutic strategy aims at controlling hormonal excess and tumour growth. However, as complete tumour eradication by surgery is achieved in <50% of the patients with sporadic tumours, and in almost none of the patients with MEN 1, unless extensive surgery is performed, long-term treatment of the excessive gastrin secretion and its sequelae is mandatory (Jensen *et al.* 2012). Traditionally, this has been achieved with the use of medications that counteract gastrin-induced hyperchlorhydria such as histamine-2 receptor (H2R) antagonists and PPIs; H2R antagonists (cimetidine and ranitidine) were first used, but due to their short duration of action (<8–15h), acid hypersecretion was not adequately controlled, necessitating substantial dose escalation (Schubert & Peura 2008). Currently, PPIs are regarded as first-line treatment due to their prolonged duration of action (3–4 days) and potent inhibition of gastric acid hypersecretion in the majority of patients with ZES (Nieto & Pisegna 2006, Jensen *et al.* 2012). High initial doses of PPIs (such as 60–80mg/day of omeprazole) are frequently prescribed, with dose adjustment as necessary based on symptom response. Additionally, the dose can also be titrated to reduce the acid hypersecretion to ≤ 10 mEq/h, or to lower values in patients with previous acid-reducing surgery or severe

reflux disease (Ito *et al.* 2013). Long-term treatment with PPIs has been shown to be safe with the only potential side effects being PPI-induced achlorhydria that may lead to B12 deficiency, although there is a suggestion of an increased incidence of bone fractures (Jensen *et al.* 2012). SS analogues can also reduce gastrin hypersecretion and may be used in combination with PPIs in rare patients with symptoms refractory to PPIs (Ruszniewski *et al.* 1993, Granberg *et al.* 2008). Gastrinomas are predisposed to GI perforation and haemorrhage, which may complicate surgery. During surgery, patients need adequate protection with PPIs to efficiently control the acid hypersecretion (Cisco & Norton 2007). In the acute setting where oral medications may be contraindicated, intravenous 80 mg of pantoprazole given by 15 min infusion every 8 h controlled gastric acid hypersecretion in all ZES patients studied both acutely and up to 7 days (Lew *et al.* 2000). Patients should maintain their medication with PPIs for some weeks after surgery, since many continue to hypersecrete acid for some time (Ito *et al.* 2013). Recently, oral gastrin receptor antagonists have also been synthesised that have a rapid mode of action and can induce prolonged gastric acid output suppression (Fossmark *et al.* 2012). However, their potential role in the treatment has not been investigated as PPIs have been highly active.

Glucagonoma

Patients with glucagonomas may present with troublesome skin disease (necrolytic migratory erythema) and some patients may be cachectic (Kaltsas *et al.* 2004, Kindmark *et al.* 2007). SSA treatment, amino acid infusion and antibiotics may improve the condition and heal the skin lesions in 50–90% of the patients with glucagonomas, although diabetes mellitus may not substantially improve (Doherty *et al.* 2005). In addition, parenteral nutrition may also be required to help improve concomitant cachexia, hypoaminoacidaemia and weight loss (Doherty *et al.* 2005). Patients with glucagonomas have a substantial risk of deep vein thrombosis and pulmonary embolism, and should perioperatively receive prophylactic high-dose molecular heparin as anticoagulation treatment as long as the disease is active (Kaltsas *et al.* 2004, Kindmark *et al.* 2007).

VIPoma

In VIPoma patients, secretory diarrhoea is generally extensive, with severe loss of potassium and bicarbonate leading to metabolic acidosis, dehydration and

hypokalaemia (Doherty *et al.* 2005). VIPomas require meticulous control of high-volume fluid loss as this may lead to severe electrolyte abnormalities and dehydration. Long-acting SS analogues achieve control of the diarrhoea in the majority of such patients, whereas medications such as glucocorticoids, clonidine and loperamide, which were previously used, have, for the most part, been replaced by SSAs. Patients need to be resuscitated from life-threatening fluid losses and electrolyte abnormalities with SSA treatment, as well as intravenous and electrolyte therapy, before being subjected to surgery (Song *et al.* 2009). There is some evidence that sunitinib, a tyrosine kinase inhibitor, may exert a particular effect in VIP-secreting pNETs regarding symptom and biochemical control irrespective of its effect on tumour growth, and it can thus be used as an adjuvant treatment for symptomatic control in cases of SS analogue-resistant tumours (Bourcier *et al.* 2013, de Mestier *et al.* 2015b). As there is a paucity of data regarding regulation of VIP secretion by tumour cells, sunitinib may affect both cyclic adenosine monophosphate and intracellular calcium pathways that have been shown to be implicated in VIP secretion (de Mestier *et al.* 2015b). However, more information of a potential specific effect on sunitinib on VIP-secreting pNETs is required.

Somatostatinoma

Although there is no consensus regarding the true incidence of these GEP-NETs, octreotide has been shown to exert activity in cases with symptoms suggestive of an SS-secreting tumour and elevated SS levels (Angeletti *et al.* 1998).

Unknown and paraneoplastic syndromes

A number of more rare syndromes attributed to the secretion of bioactive compounds that have not been described are gradually emerging, confirming the multipotent secretory potential of NETs. Recently, a case of cholecystokinin (CCK)-secreting pNET has been identified when high CCK levels were measured in a patient with metastatic pNET, presenting with non-watery diarrhoea, severe weight loss, gallbladder and peptic ulcer disease but normal gastrin levels (Rehfeld *et al.* 2013). In addition, approximately 3–6% of the patients with pNETs were shown to secrete multiple hormones at diagnosis, obscuring the clinical phenotype (Crona *et al.* 2016, de Mestier *et al.* 2015b). There have also been some reports in the literature of apparently non-functioning pNETs that, during the course

Table 4 Paraneoplastic syndromes related to GEP-NETs.

Syndrome	Bioactive substance	GEP-NET	Features distinguishing PNS from eutopic functioning tumours and their medical management			
			Clinical/biochemical	Endocrine	Radiological	Symptomatic management
Hypercalcaemia	PTHrP PTH Growth factors/ cytokines	pNET, carcinoid	↑ Ca, ↓ P, ↑ cAMP urine	↓ PTH, ↑ PTHrP ↑ PTH ↑ TGFβ, ↑ IL, ↑ PG	Parathyroid imaging (–) CT elsewhere (+) SRS (+)	Rehydration, bisphosphonates, calcitonin, cinacalcet, dialysis
Cushing's syndrome	ACTH CRH	pNET, carcinoid	Cushing's phenotype	↑ ACTH – isoforms ↑ CRH CRH/DDAVP test	Pituitary MRI (no adenoma) IPSS (–) CT/MRI (+) elsewhere SRS (+)	Drugs inhibiting steroidogenesis, adrenolytics SS analogues, dopamine agonists, pasireotide
Acromegaly	GHRH GH	pNET, carcinoid	Acromegaloid symptoms	↑ GH, ↑ IGF1 OGTT: no GH suppression	Pituitary MRI (no adenoma) CT/MRI (+) elsewhere SRS (+)	SS analogues, pasireotide, dopamine agonists, pegvisomant
Other pituitary hormones	LH/FSH TSH	pNET	Hyperandrogenism Hyperthyroidism	↑ LH, androgens ↑ Ft4, T3, TSH	Pituitary MRI (no adenoma) CT/MRI (+) elsewhere SRS (+)	SS analogues, dopamine agonists
Vasoactive peptides	CGRP Ct	pNET	Vasodilation Hypotension, flushing	↑ Ct Ca/pentagastrin test	Thyroid US (no nodule) CT/MRI (+) elsewhere SRS (+)	SS analogues, pasireotide
Gut hormones	Ghrelin Gastrin VIP GLP1,2	pNET/carcinoid pNET/carcinoid pNET pNET	? Phenotype ZES Pancreatic cholera ? Hypoglycaemia	↑ Ghrelin ↑ Gastrin ↑ VIP	CT/MRI (+), SRS (+) CT/MRI (+), SRS (+) CT/MRI (+), SRS (+), EUS (+) CT/MRI (+), SRS (+), EUS (+)	SS analogues, pasireotide
Hypoglycaemia	Insulin IGF1 IGF2 Pro-IGF2	Carcinoid	Autonomic and neuroglucopenic symptoms	↑ Insulin ↑ IGF1 ↑ IGF2 ↑ pro-IGF2	EUS (–) CT/MRI (+) elsewhere SRS (+)	SS analogues, pasireotide, everolimus, glucocorticoids, GH
Hypertension	Renin	Carcinoid	↑ Arterial pressure Hypokalaemic alkalosis	↑ Renin, aldosterone	CT adrenals (no adenoma) CT/MRI (+) elsewhere SRS (+)	SS analogues, pasireotide
Gynaecomastia/ menstrual irregularity	hCG	pNET	Gynaecomastia, menstrual irregularity Precocious puberty	↑ hCG, androgens	Normal adrenal and gonadal imaging CT/MRI (+) elsewhere SRS (+)	SS analogues, pasireotide

ACTH, adrenocorticotrophin hormone; CGRP, calcitonin gene-related peptide; CRH, corticotrophin-releasing hormone; Ct, calcitonin; CT, computerised tomography; DDAV, desmopresin; EUS, endoscopic ultrasound; FSH, follicle-stimulating hormone; Ft4, free thyroxine; GH, growth hormone; GHRH, growth hormone-releasing hormone; IGF1, insulin growth factor 1; IPSS, inferior petrosal sinus sampling; LH, luteinising hormone; MRI, magnetic resonance imaging; OGTT, oral glucose-tolerance test; PG, prostaglandins; pNET, pancreatic neuroendocrine tumour; PTHrP, parathyroid hormone-related peptide; SRS, somatostatin receptor scintigraphy; SS, somatostatin; T₃, triiodothyronine; TGFβ, transforming growth factor; VIP, vasointestinal peptide.

of the disease, changed their phenotype into functioning tumours (Vashi *et al.* 2011, Nahmias *et al.* 2015). Although this phenomenon was originally considered to be unique to non-functioning NETs, it has also been encountered in functioning NETs that alter their secretory component from one bioactive substance to another (Ohn *et al.* 2013, Nahmias *et al.* 2015). Recently, two studies have particularly addressed this issue (Crona *et al.* 2016, de Mestier *et al.* 2015a). Metachronous hormonal syndromes developed in 15 out of 435 (3.4%) patients with pNETs after a median of 55 months (de Mestier *et al.* 2015a). Five of these 15 patients developed insulin and VIP hypersecretion, respectively, whereas the remaining showed gastrin and glucagon hypersecretion; interestingly, the Ki-67 LI increased from 7 to 17.5% at transformation (de Mestier *et al.* 2015a). In a further study, 14 of 323 (4%) patients with pNETs developed metachronous hormonal hypersecretion, whereas this phenomenon was extremely rare in 603 patients with small intestinal NETs (Crona *et al.* 2016). Median survival was reduced in patients with metachronous hormonal hypersecretion in both studies, and it was worse in those with insulin hypersecretion (Crona *et al.* 2016, de Mestier *et al.* 2015a). Since the majority of these tumours had metastasised to the liver, potential therapeutic problems may arise in cases of difficult-to-manage secretory syndromes such as insulin-secreting tumours and CS. Currently, there is limited knowledge regarding the mechanism of tumour transformation and switching in its secretory potential, although NE cells are derived from a pluripotent progenitor cell, which may exhibit considerable plasticity regarding tumour phenotype (Florio 2011). Awareness of such tumoural transformation is of utmost importance for early recognition and treatment of such patients. It is possible that such transformation might be more common than currently recognised, as some of the symptoms may not be specific and difficult to recognise in patients with extensive disease.

Occasionally, the substances secreted by GEP-NET are not directly related to the tissue of origin, the corresponding clinical syndromes being called paraneoplastic (Kaltsas *et al.* 2010). A high index of suspicion for the presence of such syndromes is required, as, if the clinical presentation is missed, it may delay the diagnosis of the underlying neoplasia and lead to increased morbidity and mortality. The most common of these syndromes encountered in patients with GEP-NETs along with their presentation and symptomatic treatment are shown in Table 4. Some of these syndromes, such as Cushing's syndrome due to ectopic adrenocorticotrophin hormone (ACTH) and hypercalcaemia due to ectopic parathyroid hormone-related peptide (PTHrP)

secretion, may significantly increase the operative risk, and need to be adequately treated before any intervention (Kaltsas *et al.* 2010, Somasundaram *et al.* 2013).

Conclusion

The symptomatic treatment of functioning GEP-NETs has markedly improved following the introduction of long-acting SSAs into clinical practice. There are, however, a number of syndromes for which cytoreductive procedures and SSAs may not be sufficient to ameliorate related symptoms, and further additive treatment is required. In patients with CS inadequately controlled, increasing the dose of the SSA or administration of top-up doses of s.c. octreotide may be needed, whereas the multiligand SSA pasireotide could be effective in patients' refractory to octreotide or lanreotide. The newly introduced serotonin synthesis inhibitor telotristat etiprate has shown to reduce further the symptoms of CS with or without concomitant SSA treatment. Occasionally, combinations of all of these drugs may be required to obtain symptomatic control and reduce the risk of developing long-term complications such as CHD, whereas intravenous continuous octreotide infusion remains the best mean to minimise the risk of carcinoid crisis. Malignant insulinomas may require combination treatment with glucose infusion and diazoxide, whereas everolimus appears to be a new specific treatment for relieving intractable hypoglycaemia. Knowledge of new emerging syndromes, and alterations of the secretory component of previously diagnosed GEP-NETs, helps identify underlying previously unsuspected syndromes in patients with extensive disease and provide appropriate treatment.

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