Editorial

Octapeptide somatostatin-analogue therapy of Cushing's syndrome

The currently available octapeptide somatostatin analogues octreotide (Sandostatin, Sandostatin LAR, Novartis, Basle, Switzerland) and somatuline (BIM 23014, Lanreotide, Beaufort-Ipsen, Paris, France) have beneficial effects in the treatment of various neuroendocrine tumour syndromes. These effects are mediated through specific membrane-associated somatostatin receptor subtypes (sst_s) on the target tissues.¹ Five different sst subtypes (sst₁₋₅) have been cloned and characterised, and it was demonstrated that octapeptide somatostatin analogues bind with a high affinity to sst₂ and sst₅, show a low affinity to sst₃, but no affinity to sst₁ and sst₄.¹ Tumours and metastases, which bear receptors for octapeptide analogues, can be visualised *in vivo* using gamma camera pictures obtained after injection of ¹¹¹In-pentetreotide (OctreoScan, Mallinckrodt, Petten, The Netherlands).¹

The possible therapeutic effects of octreotide have been studied in the different subclasses of Cushing's syndrome. Cushing's disease, which exclusively stands for the excessive secretion of (adreno)corticotropin (ACTH) by the pituitary, is the main variant of Cushing's syndrome, representing about 65–75% of patients.² The five different ssts can be expressed by human corticotrophs.³ Studies in cultured human ACTH-secreting tumour cells have demonstrated that basal and corticotropin-releasing-factor-stimulated ACTH release was only inhibited by somatostatin or octreotide if the cells were pre-cultured in a medium without glucocorticoids.^{4–5} In line with this, no suppressive effect of octreotide has been demonstrated in the majority of patients with untreated Cushing's disease, who have increased cortisol levels.⁶ In our experience, none of eight ACTH-secreting pituitary microadenomas and one macroadenoma showed an increased uptake of ¹¹¹In-pentetreotide *in vivo*. However, ¹¹¹In-pentetreotide scintigraphy (SRS) was positive for two invasive ACTH-secreting macroadenomas.⁷ In contrast, octapeptide somatostatin analogues are potent inhibitors of ACTH hypersecretion in patients with Nelson's syndrome and patients treated for

adrenal insufficiency who are on cortisol replacement therapy only.^{8–11} We have also reported positive SRS in the cases of two Nelson tumours.⁷ The results in patients with Cushing's disease might be explained by somatostatin receptor down-regulation by hypercortisolaemia.

A variety of non-pituitary tumours are capable of ectopic secretion of proopiomelanocortin-derived peptides. These account for 10–20% of patients with Cushing's syndrome.² Small cell lung cancer and bronchial carcinoid tumours are the commonest source of ectopic ACTH-secretion. Up to now, more than 45 cases of ectopic ACTH syndrome treated with octreotide have been reported in more than 30 studies in the medical literature. After an acute challenge with octreotide, or following short- or long-term octreotide therapy, ACTH levels decreased in most patients, or remained the same in some patients. In incidental cases, a paradoxical increase of ACTH was observed after the administration of octreotide.^{12–13} Insensitivity of neuroendocrine tumours to octreotide develops in some patients, which is probably due to a preferential outgrowth of sst-negative tumour cell clones, or down-regulation of ssts.¹⁴

The localisation of an ectopic source of ACTH hypersecretion may sometimes cause diagnostic problems. In particular, bronchial carcinoid tumours may prove extremely hard to localise. Even with the use of advanced computed tomography and magnetic resonance imaging protocols, small carcinoids can be easily confused with pulmonary vascular contours.¹⁵

It may also be necessary to perform extensive scanning of the abdomen in the presence of negative imaging of the chest.¹⁵ Ourselves and others have shown that SRS can disclose occult lesions that were initially not visualised with conventional radiological techniques (table).^{16–29} When somatostatin analogue therapy is considered, this technique may also be used to confirm the presence of functional receptors for octapeptide somatostatin analogues as demonstrated in the study by Gill and co-workers elsewhere in this issue.^{1–29} SRS may have a negative impact on tumour staging and modification of (pre-operative and/or postoperative) management will be necessary in some of these cases.¹ SRS might also be used in the follow-up of curatively operated patients, to detect regrowth of tumour remnants or newly occurring metastases at an early stage.¹ However, it is important to keep in mind that, although this technique has a very high sensitivity for octapeptide receptor-positive tumours, its specificity is low.¹ Also, in rare cases, tumours expressing specific ssts and tumours that do not express these receptors and therefore do not bind radiolabeled octreotide, may co-exist in the same patient.^{1–11} ¹¹¹In-Pentetreotide can also be used in combination with a hand-held radionuclide probe for intra-operative scanning in search of tumour deposits.²³

Benign or malignant adrenocortical tumours are the most common cause of ACTH-independent Cushing's syndrome, and can be found in 5–20% of patients with Cushing's syndrome.² In contrast to animal studies, studies determining the sst status of human adrenocortical tumours are still lacking. SRS is usually not positive in all variants of the ACTH-independent Cushing's syndrome. However, in 1995, Pandha and co-workers described, in

Table Pentetreotide scintigraphy for the detection of occult ectopic ACTH-secreting tumours

Reference	Primary tumour	Scan	Tumour diameter (mm)	Metastases	
				Present	Visualised
16	bronchial carcinoid	+	10×15	+	+
16	bronchial carcinoid	+	12×18	–	–
17	bronchial carcinoid	+	10	+	–
18	bronchial carcinoid	+	6	–	–
19	bronchial carcinoid	+	9	–	–
20	bronchial carcinoid	+	6	–	–
21	bronchial carcinoid	+	20	–	–
22	bronchial carcinoid	+	15	–	–
23	bronchial carcinoid	+	15×18	–	–
24	bronchial carcinoid	+	13	–	–
25	bronchial carcinoid	+	6	–	–
26	thymic carcinoid	+	15×20	–	–
27	ileal carcinoid	+	?	+	+
28	carcinoid, unknown primary localisation	–	?	?	?
16	carcinoid, unknown primary localisation	–	?	?	?
29	carcinoid, unknown primary localisation	+	?	+	+

this journal, a favourable cortisol response to octreotide therapy in a patient with a cortisol-secreting adrenocortical carcinoma.³⁰ Chan and co-workers could not reproduce these findings in a similar case, also reported elsewhere in this issue.³¹ The therapeutic use of octreotide in ACTH-independent Cushing's syndrome has not yet been clearly established.

Food-dependent, gastric inhibitory polypeptide (GIP)-dependent Cushing's syndrome is a particularly rare cause of ACTH-independent Cushing's syndrome. In these patients, octreotide may only temporarily suppress non-

pathological meal-induced GIP release, thereby suppressing GIP-induced cortisol secretion.³²

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