Is There a Role for Somatostatin and Its Analogs in Cushing's Syndrome?

W.W. de Herder and S.W.J. Lamberts

The effects of somatostatin and its analogs have been studied in different subclasses of patients with Cushing's syndrome (due to Cushing's disease, ectopic corticotropin [ACTH]- and/or corticotropin-releasing hormone [CRH]-secreting tumors, or ACTH-independent Cushing's syndrome) and in patients with Nelson's syndrome. In most patients with untreated Cushing's disease, octreotide does not suppress ACTH release, a finding that is supported by in vitro studies. However, octreotide or somatostatin inhibits pathological ACTH secretion in Nelson's syndrome. Short-term octreotide treatment has caused a significant initial response (decreased serum cortisol, ACTH, and cortisoluria) in 24 of 38 (64%) patients with ectopic ACTH/CRH Cushing's syndrome, and long-term treatment caused a persistent response in 10 of 14 (71%) cases. Pentetreotide scintigraphy may help to identify those patients with ectopic ACTH/CRH tumors who will have an initial response to octreotide, and is useful for locating ectopic ACTH/CRH-secreting tumors and their metastases. To date, octreotide has been shown to temporarily suppress gastric inhibitory peptide (GIP)-induced cortisol secretion in GIP-dependent (ACTH-independent) Cushing's syndrome, but has not shown any therapeutic benefit in other forms of ACTH-independent Cushing's syndrome.

SOMATOSTATIN and its analogs have beneficial effects in the treatment of various endocrine tumors. It is therefore not surprising that the effects of these drugs have been studied in the different subclasses of patients with Cushing's syndrome and in patients with Nelson's syndrome. Cushing's syndrome can be separated into the categories of corticotropin (ACTH)-dependent and ACTH-independent Cushing's syndrome.[1]

Cushing's disease, a term reserved exclusively for the excessive secretion of ACTH by the pituitary, is the main variant of the syndrome, representing approximately 65% to 75% of patients.[1] Nelson's syndrome develops in 8% to 45% of patients following biadrenalectomy, usually for Cushing's disease. It is characterized by widespread skin hyperpigmentation, marked elevation of plasma ACTH levels, which is relatively resistant to low doses of glucocorticoids, and a pituitary tumor, usually a macroadenoma.[2]

Recent studies show that the five different somatostatin receptor subtypes can be expressed by human corticotrophs.[3] Studies in cultured normal rat pituitary cells and human pituitary tumor cells have demonstrated that basal and corticotropin-releasing hormone (CRH)-stimulated ACTH release is only inhibited by somatostatin or octreotide if the cells are precultured 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 contrast, in patients with Nelson's syndrome, who are only on cortisol-replacement therapy, long-term inhibition of pathological ACTH secretion by somatostatin and octreotide has been demonstrated.[6] This is sometimes accompanied by stabilization of tumor growth and restoration of visual-field defects. Similarly, pituitary tumors of patients with Nelson's syndrome, but not those of patients with Cushing's disease, show an increased uptake of the radiolabeled somatostatin analog pentetreotide in vivo.[7] The results in patients with Cushing's disease and Nelson's syndrome might be explained by somatostatin receptor downregulation by cortisol in the hypercortisolemic state.[3]

A variety of nonpituitary tumors are capable of ectopic secretion of pro-opiomelanocortin (POMC)-derived peptides. Such tumors account for 10% to 20% of patients with Cushing's syndrome.[1] Only a few cases of ectopic CRH-secreting tumors have been reported, and, in most of these cases, ectopic cosecretion of ACTH has also been demonstrated.[1,7]

Table 1. Ectopic ACTH-Secreting Tumors Treated With Octreotide

Primary Tumor	No.	Initial Response	Prolonged Response
Bronchial carcinoid	11	8/11	3/4
Thymic carcinoid	3	1/3	
Pancreatic carcinoid	2	0/2	
Carcinoid of unknown primary	2	0/2	
Islet-cell tumor	9	8/9	4/5
Medullary thyroid carcinoma	2	2/2	1/1
Small-cell lung cancer	2	1/2	
Adenocarcinoma of the lung	1	0/1	
Hepatocellular carcinoma	1	1/1	
Occult tumor	5	3/5	2/4
Total	38	24/38	10/14
Percentage of responders		64	(71)

NOTE. Data taken from the results of studies reported in 25 published reports.

Until now, approximately 38 cases of the ectopic ACTH and/or CRH syndrome treated with somatostatin (analogs) have been reported in 25 published reports or abstracts. A significant initial response, defined as a greater than 30% decrease in serum cortisol, cortisoluria, or serum ACTH levels after up to 3 days of octreotide treatment, or in an acute test, has been observed in 24 of 38 patients (64%) with the ectopic ACTH syndrome.[7,8] A prolonged response to octreotide (defined as a persistent decrease in serum cortisol, cortisoluria, or serum ACTH levels of greater than 30% for greater than 3 months) has only been reported in 10 of 14 cases (71%)[7] (Table 1).

From the Department of Internal Medicine III, University Hospital Rotterdam, Rotterdam, The Netherlands.

Address reprint requests to W.W. de Herder, MD, Department of Internal Medicine III, University Hospital Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

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Table 2. Pentetreotide Scintigraphy for the Detection of Occult Ectopic ACTH-Secreting Tumors

Author, Year	Primary Tumor	Scan	Tumor Diameter (mm)	Metastases	
				Present	Visualized
de Herder et al, 1994[7]	Bronchial carcinoid	+	10 × 15	+	+
de Herder et al, 1994[7]	Bronchial carcinoid	+	12 × 18	–	–
Lefebvre et al, 1995[8]	Bronchial carcinoid	+	9	–	–
Mazza et al, 1994[9]	Bronchial carcinoid	+	12	–	–
Weiss et al, 1994[10]	Bronchial carcinoid	+	10	+	–
Phlipponneau et al, 1994[12]	Bronchial carcinoid	+	6	–	–
Madhun et al, 1995[13]	Epigastric, neuroendocrine?	+	?	?	–
Bitton et al, 1995[14]	Pancreatic islet cell	+	25	–	–
de Herder et al, 1994[7]	Carcinoid, localization?	–	?	?	
Lastowiecki & Kreisberg 1994[11]	Carcinoid, localization?	–	?	?	

As in all nonsomatotroph tumors, it seems that insensitivity of the tumors to octreotide develops with time. This might be due to a selection of somatostatin receptor–negative tumor cell clones. The initial sensitivity of these tumors to somatostatin analogs depends on the expression of high numbers of specific somatostatin receptor subtypes.[8] Pentetreotide scintigraphy may be helpful for selecting those cases that indeed express these receptors. Furthermore, this technique has been successful for the localization of ACTH- and CRH-secreting tumors and their metastases, especially in those difficult cases in which conventional radiological studies had initially failed to localize the tumors. Reviewing the published results so far, eight of 10 occult tumors secreting ACTH ectopically could be visualized by this technique[8-14] (Table 2).

Benign or malignant adrenocortical tumors are the most common cause of ACTH-independent Cushing's syndrome, and can be found in 5% to 20% of patients with Cushing's syndrome. Rare causes of ACTH-independent Cushing's syndrome include ACTH-independent bilateral micronodular and macronodular hyperplasia and gastric inhibitory polypeptide (GIP)-dependent Cushing's syndrome.[1] In the latter case, illicit expression of GIP receptors on adrenal cells possibly causes an abnormal responsiveness to physiological levels of GIP.[15-17] Until now, somatostatin receptor scintigraphy has been negative in all variants of the ACTH-independent Cushing's syndrome.[7] In GIP-dependent Cushing's syndrome, octreotide only temporarily suppresses nonpathological meal-induced GIP release, thereby suppressing GIP-induced cortisol secretion.[15-17] To date, no therapeutic effects of octreotide have been reported in ACTH-independent Cushing's syndrome with other causes.

CONCLUSIONS

(1) Pentetreotide scintigraphy is not useful for the differential diagnosis of ACTH-dependent Cushing's syndrome, as a minority of occult tumors that secrete ACTH ectopically may not take up the radioligand.

(2) Pentetreotide scintigraphy is useful in patients with established ectopic ACTH secretion for (early) detection of primary and metastatic tumor sites and for selection of patients for octreotide therapy.

(3) Octreotide therapy may be useful in the initial therapy of selected (pentetreotide scan–positive) patients with the ectopic ACTH syndrome.

(4) Octreotide therapy is not useful in patients with Cushing's disease.

(5) Octreotide therapy may be useful in selected (pentetreotide scan–positive) patients with Nelson's syndrome.

(6) Octreotide therapy in ACTH-independent Cushing's syndrome is only of temporary benefit in patients with the GIP-dependent Cushing's syndrome.

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