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 (SSTs) on the target tissues. 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, and with a low affinity to SST1, but no affinity to SST3 and SST4.1 Tumours and metastases, which bear receptors for octapeptide analogues, can be visualised in vivo using gamma camera pictures 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 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.5 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.6 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.6,7 We have also reported positive SRS in the cases of two Nelson tumours.1 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.16 Ourselves and others have shown that SRS can disclose occult lesions that were initially not visualised with conventional radiological techniques (table).16–20 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.11 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 radiolabelled octreotide, may co-exist in the same patient.11,12 In-Pentetreotide can also be used in combination with a hand-held radionuclide probe for intra-operative scanning in search of tumour deposits.13 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.1 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>
<thead>
<tr>
<th>Reference</th>
<th>Primary tumour</th>
<th>Scan</th>
<th>Tumour diameter (mm)</th>
<th>Metastases</th>
<th>Present</th>
<th>Visualised</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>10±15</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>12±18</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>17</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>10</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>6</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>19</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>9</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>20</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>6</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>21</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>20</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>22</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>15</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>23</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>15±18</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>24</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>13±15</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>25</td>
<td>bronchial carcinoid</td>
<td>+</td>
<td>6</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>26</td>
<td>thymic carcinoid</td>
<td>+</td>
<td>15±20</td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>27</td>
<td>ileal carcinoid</td>
<td>+</td>
<td>7±2</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>28</td>
<td>carcinoid, unknown</td>
<td>–</td>
<td>?</td>
<td></td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>29</td>
<td>primary localisation</td>
<td>?</td>
<td>?</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Editorial

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

pathological meal-induced GIP release, thereby suppressing GIP-induced cortisol secretion.¹²

W W DE HERDER
S W J LAMBERTS
Department of Internal Medicine III, University Hospital Rotterdam,
Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

Accepted 3 November 1998

Keywords: somatostatin analogues; octreotide; Cushing’s syndrome

Octapeptide somatostatin-analogue therapy of Cushing's syndrome

W W DE HERDER and S W J LAMBERTS

doi: 10.1136/pgmj.75.880.65

Updated information and services can be found at:
http://pmj.bmj.com/content/75/880/65

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
- Drugs: CNS (not psychiatric) (99)
- Adrenal disorders (17)
- Screening (oncology) (91)
- Clinical diagnostic tests (395)
- Radiology (418)
- Radiology (diagnostics) (291)
- Lung cancer (oncology) (17)
- Lung cancer (respiratory medicine) (17)
- Pituitary disorders (13)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/