Imaging secondary neuroendocrine tumours of the liver: comparison of I\textsuperscript{123} metaiodobenzylguanidine (MIBG) and In\textsuperscript{111}-labelled octreotide (Octreoscan)

J.K. RAMAGE, R. WILLIAMS and M. BUXTON-THOMAS

From the Institute of Liver Studies and Department of Nuclear Medicine, King's College Hospital, London, UK

Received 7 November 1995 and in revised form 14 March 1996

Summary

Functional imaging of neuroendocrine tumours with Octreoscan and I\textsuperscript{123}-metaiodobenzylguanidine (MIBG) is important for assessment prior to various therapies and assessing response. The two imaging methods have not been directly compared in hepatic neuroendocrine tumours. Patients (n = 18) were studied with both imaging techniques. The sensitivity of Octreoscan was 94\%, and that of MIBG 39\%. No previously occult primary sites were detected.

Concurrent octreotide therapy did not reduce the sensitivity of Octreoscan. Widespread bone metastases were seen in two post-liver-transplant patients using Octreoscan. Octreoscan is a sensitive means of detecting hepatic neuroendocrine tumours, and the more specific technique. MIBG has poor sensitivity, reducing its clinical utility. Therapy with I\textsuperscript{131}-MIBG is likely to be applicable to relatively few patients.

Introduction

Functional imaging of neuroendocrine tumours has become possible as a result of two characteristics of the tumour cells. The first is that they express somatostatin receptors and therefore can be imaged with Indium\textsuperscript{111}-labelled octreotide (Octreoscan).\textsuperscript{1-4} The second characteristic of neuroendocrine tumours is that amine precursors are taken up into the cells by a specific amine precursor uptake/decarboxylase (APUD) pathway. Labelling of physiological amine precursors was unsuccessful, but metaiodobenzylguanidine (MIBG) is taken up by the same pathway and is concentrated in tumours cells, and thus I\textsuperscript{123}-labelled MIBG can be used for imaging.\textsuperscript{5-7} Furthermore, tumours which concentrate MIBG on scanning may respond to local radiation therapy with I\textsuperscript{131} MIBG.\textsuperscript{8-10} Imaging is becoming increasingly important in order to document extrahepatic spread in those considered for hepatic surgery\textsuperscript{11} transplantation\textsuperscript{12,13} or for monitoring responses to chemotherapy.\textsuperscript{14}

In the present study, octreotide and MIBG scanning were directly compared in 18 patients with neuroendocrine tumours of the liver to determine the relative accuracy and clinical value of the two methods.

Methods

The 18 patients studied had either histologically-proven neuroendocrine tumours of the liver (by chromogranin staining and histological appearance) or positive urinary 5HIAA (at least three times normal range). Two of the patients (2 and 5) were scanned for the first time after liver transplant which had been performed for severe symptoms unresponsive to medical therapy.

All patients adhered to a standard protocol. Potassium iodate was administered 24 h prior to MIBG to block thyroid uptake. On day 1, 185 MBq I\textsuperscript{123} MIBG was given intravenously with scanning at...
4 and 24 h. Immediately following the last MIBG scan, the subject was injected with 120 MBq In\(^{111}\)-DTPA-D-Phe-Octreotide with planar whole-body scans acquired at 24 and 48 h using an ADAC dual-head Genesys system. Single-photon emission tomography (SPET) was used for all patients and this is particularly important for Octreoscan images since the octreotide In\(^{111}\) is concentrated in renal tissue which may overlie tumour. Scans were interpreted by two independent observers.

Results

In 17 (94%) of the 18 patients, definite lesions within the liver were demonstrable with Octreoscan (Table 1). The one patient (patient 4) in which no liver lesion was identified by Octreoscan had Carney’s triad\(^{15}\) (of gastrointestinal leimyoma, pulmonary chondroma and extra-adrenal apudoma) in which the neuroendocrine tumour of the liver may be atypical.

In 5/18 patients, Octreoscan identified a primary site although in all of these this site was previously known (Figure 1). In a further two cases with a known primary site this was not demonstrated by the Octreoscan. The known primary sites in these seven patients had previously been picked up by CT scanning of the pancreatic primary sites (four patients), and by small bowel barium studies (two patients) or laparotomy (one patient) in the cases with ileal lesions.

In the two patients (2 and 5) studied post-transplant, widespread bony metastases were seen as a result of tumour recurrence, and these had not been previously diagnosed. Both had liver lesions in addition to bony metastases (Figure 2). Ten of the patients were studied with Octreoscan while they were concurrently taking octreotide for relief of symptoms and this appeared not to interfere with uptake of the isotope within tumour.

Using MIBG scanning, only seven (39%) of the 18 cases had positive uptake within the liver lesions. Two of the primary sites were also positive for MIBG (Figure 2). In two further cases, photon-deficient areas were clearly seen within the liver, and the same lesions had been photon-dense on Octreoscan. None of the bone lesions in patients 2 and 5 shown on Octreoscan were positive with MIBG. In only two patients (10 and 11) were primary sites seen using MIBG, and no previously occult primary sites were revealed by this method.

Discussion

This study has confirmed the clinical use of Octreoscan scintigrams in defining intrahepatic neuroendocrine tumours shown previously.\(^{3,4,7,16}\) and also in detecting extrahepatic spread. The sensitivity for detecting hepatic lesions using Octreoscan was 94%, rather better than the overall figures (for pooled results of 451 patients from all published series by 1994) of 86%.\(^{7}\) This imaging method is particularly

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical</th>
<th>Primary site</th>
<th>Octreotide liver</th>
<th>Octreotide primary</th>
<th>MIBG liver</th>
<th>MIBG primary</th>
<th>On Octreotide?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Secreting carcinoid</td>
<td>NK</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>y</td>
</tr>
<tr>
<td>2</td>
<td>Post OLT recurrence</td>
<td>Panc</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>n</td>
</tr>
<tr>
<td>3</td>
<td>Secreting carcinoid</td>
<td>NK</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>y</td>
</tr>
<tr>
<td>4</td>
<td>Non-secreting apudoma</td>
<td>Stomach</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n</td>
</tr>
<tr>
<td>5</td>
<td>Post OLT recurrence</td>
<td>Anus*</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
</tr>
<tr>
<td>6</td>
<td>Secreting carcinoid</td>
<td>Ileum</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
</tr>
<tr>
<td>7</td>
<td>Secreting carcinoid</td>
<td>NK</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>y</td>
</tr>
<tr>
<td>8</td>
<td>Non-secreting carcinoid</td>
<td>Pancreas*</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n</td>
</tr>
<tr>
<td>9</td>
<td>Secreting carcinoid</td>
<td>Ileum*</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>y</td>
</tr>
<tr>
<td>10</td>
<td>Secreting carcinoid</td>
<td>Ileum</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>y</td>
</tr>
<tr>
<td>11</td>
<td>Secreting carcinoid</td>
<td>Ileum</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>y</td>
</tr>
<tr>
<td>12</td>
<td>Non-secreting apudoma</td>
<td>Pancreas</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n</td>
</tr>
<tr>
<td>13</td>
<td>Secreting carcinoid</td>
<td>Pancreas</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>y</td>
</tr>
<tr>
<td>14</td>
<td>Secreting carcinoid</td>
<td>NK</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>y</td>
</tr>
<tr>
<td>15</td>
<td>Secreting carcinoid</td>
<td>NK</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n</td>
</tr>
<tr>
<td>16</td>
<td>Non-secreting apudoma</td>
<td>Pancreas</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n</td>
</tr>
<tr>
<td>17</td>
<td>Non-secreting apudoma</td>
<td>NK</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n</td>
</tr>
<tr>
<td>18</td>
<td>Secreting carcinoid</td>
<td>Ileum*</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n</td>
</tr>
</tbody>
</table>

*Resected prior to scan.
NK, not known; OLT, orthotopic liver transplantation.
Imaging secondary neuroendocrine tumours

Anterior Posterior
Linear

Figure 2. Patient 5 (post transplant recurrence of tumour). Octreoscan images at 24 h showing an enlarged liver with abnormal uptake and multiple hot spots throughout the pelvis and spine.

important prior to liver transplantation, which is now an accepted therapy for these tumours. When bone metastases occur, these are easily detected by Octreoscan, and the whole-body imaging facility makes it more useful than other imaging techniques in this respect. Octreoscan is not as sensitive at detecting sites of the primary tumour. Only 5/7 known primary lesions were detected by Octreoscan, and this did not identify any additional primary sites that were occult by other imaging methods.

Single photon emission tomography (SPET) scanning was shown to be important for correctly identifying liver metastases and separating these from the appearance of normal renal uptake. Areas within the hepatic tumours that accumulate labelled octreotide but leave photon-deficient areas on MIBG scans are of uncertain significance as yet. Concurrent administration of octreotide prior to scanning may improve visualization of lesions, as previously described.

Octreoscan is an important investigation for

and also a large primary site in the ileum (arrow). Uptake in the right kidney is seen to partially overlie the liver on posterior view. b MIBG images at 24 h showing uptake within the liver and the primary site (arrow) which were not as clearly demonstrated as with Octreoscan.

Figure 1. Patient 11. a Octreoscan image at 24 h anterior view (L) and posterior view (R) showing one liver lesion

Figure 1. Patient 11. a Octreoscan image at 24 h anterior view (L) and posterior view (R) showing one liver lesion

Figure 1. Patient 11. a Octreoscan image at 24 h anterior view (L) and posterior view (R) showing one liver lesion

Figure 1. Patient 11. a Octreoscan image at 24 h anterior view (L) and posterior view (R) showing one liver lesion

Figure 1. Patient 11. a Octreoscan image at 24 h anterior view (L) and posterior view (R) showing one liver lesion
detecting skeletal metastases, and will be useful in detecting such recurrent tumour after liver transplantation. The Octreoscan appearances of widespread metastases in post-liver-transplant patients has not been previously described. It is possible that immunosuppression changes the normal behaviour of the tumour, since asymptomatic widespread bony metastases are unusual in non-transplanted patients.

Imaging with labelled MIBG in this series has shown adequate visualization of metastases in only 39% of those scanned, and is clearly not useful in diagnosis of the primary tumours. This figure is lower than that of other series—6/7 lesions were positive in Bomanji’s series but only 70% of 275 patients accumulated from other publications. In the present series, only scans that had very clear lesions in the liver were considered positive, which may explain some of the differences. In those that are positive, therapy using I-131 MIBG may be possible, making this a useful investigation for that reason alone.

In clinical use, the two techniques may be complementary. Octreoscan is more sensitive, but less specific since it would be positive in many other types of tumour—e.g. small-cell lung cancer or metastatic breast cancer. Overall dosimetry with the two techniques is similar but with different distribution of absorbed dose. That of Octreoscan presents a larger dose to renal tissue. In view of the greater sensitivity of octreotide uptake into these tumours, the possibility of a therapeutic radiolabel being attached to the octreotide molecule has been addressed. Currently this has not been used clinically and some concerns exist with respect to radiation doses to the kidney and pituitary.

MIBG scanning gives more information about possible therapy and is more specific. Currently, targeted radiotherapy with I-131 is still under trial for neuroendocrine liver tumours, although it may have clearer role in the treatment of phaeochromocytoma. The therapy has not produced objective reduction in tumour size in significant numbers of patients but may have a role in reducing hormone secretion.

Our results show that only a relatively small proportion of patients could be treated in this way.

References