New techniques in medicine

Octreotide scanning for carcinoid tumours

Mair Critchley

Carcinoid tumours arise from neuroendocrine cells throughout the body and occur most frequently in the gastrointestinal tract. Primary carcinoids may occur in the area of the embryonic foregut (including thyroid, bronchus, stomach, common bile duct and pancreas), midgut or hindgut. They may also originate in the testes or ovaries. Wherever they occur, they are capable of producing one or more of the following substances: serotonin (5-hydroxytryptamine), histamine, kinin peptides, catecholamines, glucagon and gastrin. Most of the tumours are benign, non-secretory and are discovered accidentally on histological examination of appendectomy or biopsy specimens. Ten per cent of tumours, mostly arising within the midgut, are active secretors of serotonin and of these tumours 50% will have metastasized to the liver with the bizarre consequences and manifestations of the carcinoid syndrome: a sensation of intense heat and wheezing, flushing, tachycardia, hypotension with the development of endocardial fibrosis, or profuse diarrhoea accompanied by electrolyte disturbances. Carcinoid tumours of the gut do not produce metabolic symptoms when the tumour drains through an intact liver. The development of metastases is an essential requirement for the presentation of the carcinoid syndrome. Furthermore, the heterogenous nature of carcinoid tissue is such that the variety of peptide products secreted may be associated with other syndromes, additional to or separate from the classical carcinoid syndrome.

Localisation of metastases within the liver is rarely a problem. Such metastases are readily visualised by ultrasonography or computed tomography (CT). Small bowel carcinoids, which may appear as small, yellow, firm nodules of epithelial cells set in a fibrous stroma within the intestinal wall, and metastases at other sites, are more difficult to detect prior to surgery. For this reason a more physiological imaging approach is required.

The proliferation and activity of neuroendocrine tissue within the intestine and elsewhere is normally controlled by specific neuropeptides, so called because they were originally discovered in brain tissue. However, the next highest concentration of identical peptides with similar properties occurs within intestinal tissues. These peptides have largely inhibitory functions 'down-regulating sensitive cells', become attached to specific receptors binding to the cell membranes, and activate second messengers before being internalized as a receptor–ligand complex within the cells.

Radionuclide imaging

Over recent years, nuclear physicians have utilised the hormonal and physiological properties of neuropeptides, developing radiolabelled analogues as tracer-imaging radiopharmaceuticals, to detect specific binding sites. The use of peptide radiopharmaceuticals in diagnosis has been described as a 'ticket to ride'. Carcinoid and other neuroendocrine tumours can be identified as possessing an increased density of receptor-binding sites to somatostatin – a naturally occurring cyclic polypeptide hormone.

Somatostatin consists of 14 amino acids (figure 1) but is impracticable for radiolabelling because of its limited half-life (T½ 2–4 min). The advantage of somatostatin analogues, which have similar pharmacological properties to somatostatin, is their slower clearance from the circulation. The first analogue to be developed was octreotide with a sequence of eight amino acids (figure 1). Like the natural hormone, it has inhibitory actions on the pituitary gland, on gastric motility and on hormone release from neuroendocrine tissues within the gastrointestinal tract. Octreotide has been used therapeutically for the suppression of pituitary and intestinal endocrine tumours. By virtue of its longer half-life (T½ 90–120 min) it may be labelled for radionuclide imaging.

With certain modifications, it is possible to label octreotide with both 123Iodine and 111Indium. 123I-Labelled Tyr-3 octreotide is more suitable for labelled imaging.
Carcinoid tumours

- arise from neuroendocrine cells throughout the body, most frequently in the gastrointestinal tract
- 10% arise within midgut and actively secrete serotonin
- carcinoid syndrome, due to hypersecretion of serotonin (wheezing, flushing, tachycardia, hypotension), arises in carcinoids which metastasize to liver
- small bowel carcinoids are difficult to detect before surgery, and require physiological imaging approach
- carcinoids can be identified by radionuclide imaging (detection of increased density of receptor binding sites to somatostatin)

Box 1

Radiolabelled octreotides

- 111In-DTPA-octreotide
  - difficult labelling chemistry
  - limited availability of 111In (cyclotron produced)
  - T1/2 of 111In is 13 hours (not suitable for delayed imaging)
  - rapidly cleared via hepato-biliary system
  - high background tracer levels make images more difficult to interpret

- 131I-DTPA-D-Phe1-octreotide
  - easier labelling chemistry (octreotide conjugated with DTPA) enabling chelation with 131I
  - T1/2 of 131I is 2.8 days (suitable for delayed imaging)
  - clearance via renal system
  - low background interference easier image interpretation

Box 2

Imaging method

- intravenous 111In-pentetreotide: planar 111 MBq, SPECT 185 MBq
- discontinue (cold) octreotide therapy three days before tracer injection

Box 3

111In-LABELLED OCTREOTIDE

The development of 111In-labelled octreotide involved the incorporation of the chelate diethylaminoethyl-penta-acetic acid (DTPA) to the 111Indium label. The current radiopharmaceutical of choice is 111In-DTPA-DPhe1-octreotide (111In-DTPA-pentetreotide, Octreoscan®, Mallinckrodt). 111Indium has a T1/2 of 2.8 days and the radiopharmaceutical is excreted via the kidneys. The imaging protocol involves the patient stopping any 'cold' (non-radiolabelled) octreotide medication three days prior to the study in order to allow access of the radiolabelled tracer to receptor sites and so enhance the localisation of any carcinoid tissue. Failure to stop octreotide medication, however, may not completely suppress activity since many carcinoids with excess somatostatin receptor densities can remain visible to detection during octreotide treatment, although ultimate uptake of the radiopharmaceutical tracer of less than 50% may render imaging suboptimal.

Following an intravenous injection of 111 MBq 111In-DTPA-pentetreotide, planar or three-dimensional SPECT images are taken at 4 hours and 24 hours using a gamma camera linked to a computer system. Normally the tracer is visible in the thyroid, liver, gall bladder, kidneys, spleen and bladder (figure 2). With the exception of the spleen and kidneys, the physiological uptake by these organs is diffuse, and there is little interference with image interpretation. Carcinoid tumours may be seen at 24 hours more clearly than at four hours by virtue of reduction in background activity (figures 3, 4). Occasionally, 48-hour images are required, particularly if the receptor density within the tumour is relatively low.

Five different somatostatin receptor types have been recognised. Octreotide binds with high affinity to receptor subtype 2. Octreotide scintigraphy is thus based on the visualisation of octreotide-binding somatostatin receptors.

The high sensitivity (over 90%) of the technique in demonstrating carcinoid tumour sites has been shown repeatedly. However, some carcinoid tumours exist with a limited number of somatostatin-receptor sites and a lower affinity for octreotide. This receptor subtype has been observed in <10% of carcinoids as well as in other neuroendocrine tumours. Liver metastases from carcinoid tumours are sometimes not easily distinguishable from normal liver tissue on octreotide scintigraphy as the metastases may accumulate the same amount of tracer as the surrounding liver tissue. In this eventuality subtraction techniques using 99mTc colloid and SPECT imaging are helpful in diagnosis.

Octreotide scanning is useful to demonstrate the extent of tumour spread in patients with metastatic disease, particularly if liver transplantation is contemplated. The demonstration of somatostatin receptor positive tumours by octreotide scanning may be used to select those patients with carcinoid who are likely to respond favourably to 'cold' octreotide therapy. Octreotide scintigraphy may also be performed in patients whose primary carcinoid tumour has been surgically removed but whose symptoms have returned. Recognition of the high sensitivity of octreotide scanning has prompted its further use intraoperatively. Forty-eight hours after an injection and preliminary imaging with radiolabelled octreotide, a hand-held gamma ray detection probe succeeded in

Figure 2 A normal octreotide scan. A & B, planar images taken 4 h after intravenous injection of 111In-DTPA-pentetreotide, C & D after 24 h (A & C anterior view, B & D posterior view). A normal distribution of tracer can be seen in liver, spleen, kidneys and bladder with no abnormal distribution of tracer.
Figure 3 Abnormal octreotide scan showing carcinoid tumour of bronchus in the posterior thorax 24h after intravenous injection of 111In-DTPA-pentetreotide. (A) Anterior thoracic view, (B) posterior thoracic view. The lesion is seen as a "hot" spot in the posterior thorax in the lower zone of the left lung. (The patient was a 42-year-old man with buffalo hump and Cushingoid appearance. MRI pituitary, CT adrenals, chest X-ray and bronchoscopy were all normal. A subsequent CT scan confirmed a lesion in left lung. At surgery a 2cm carcinoid was removed)

Figure 4 Abnormal scan using 111In-DTPA-pentetreotide showing carcinoid of rectum with widespread metastases. (A) Posterior thoracic view, (B) anterior pelvic view, (C) anterior abdominal view, and (D) left profile. The 24 hour planar images show three hot spots in the posterior thorax (A) one in the left femur (B), multiple hot spots in the liver (C), and one in the rectum (D)

locating tumours <10 mm in size, thus improving the surgical management of the patients.14

123I-LABELLED META-IODOBENZYL GUANIDINE
An alternative radionuclide imaging technique has been described which provides physiological and functional tumour localisation – in addition to the purely anatomical localisation by ultrasound, CT and MRI. The guanethidine analogue, 123I-labelled meta-iodobenzylguanidine (MIBG), has been used to detect carcinoid and other neuroendocrine tumours. MIBG concentrates in the adrenal medulla and in the storage vesicles of carcinoid and other neuroendocrine tumours. However, the sensitivity of 123I-MIBG uptake by carcinoid is 70%15 as opposed to 96% sensitivity with octreotide.9

Therapeutic uses of radiolabelling techniques
A logical progression from radio-imaging is the use of radiolabelling techniques for therapeutic purposes using beta-ray emitters such as 131I. Patients imaged with 123I-MIBG may proceed to treatment with 131I-MIBG; a biogenic amine precursor, actively taken up in the storage cells. Response to therapy as judged by decrease in symptoms has been variably quoted as ranging from 3.8%16,17 to 60%.18 Non-radioactive octreotide will reduce symptoms of the carcinoid syndrome by receptor blocking but daily injections are required. Further developments in the therapeutic use of radiolabelled octreotide are thus awaited. Potential nephrotoxicity is a major problem and so is uptake in the pituitary gland. The incorporation of DTPA into the labelling procedure is undoubtedly an advantage for imaging with 111In-DTPA-pentetreotide. Hepatic clearance of the tracer is inhibited and renal clearance is probably facilitated. The relatively long residence time for the tracer within the kidneys, however,
suggests that part of the label is actively reabsorbed in the tubules after glomerular filtration. This could pose a problem with a radiopharmaceutical possessing a relatively long $T/2$, such as $^{111}$In ($T/2 = 8$ days).

Further studies are awaited in which concurrent administration of drugs and amino acids as well as other beta-emitters may optimise the effective use of therapeutic radiolabelled octreotide. Early animal studies using $^{147}$Terbium as a label for octreotide may show the way for further developments in the treatment of octreotide receptor positive tumours by nuclear medicine techniques.19

My thanks to Mallinckrodt Medical for allowing reproduction of figures 2–4 and to Miss L Lightwood for typing this manuscript.


9 Bomannji J, Mather S, Ur E, Grossman A, Besser GM, Britton KE. Imaging somatostatin receptor-positive neoplasms with $^{111}$In-DTPA-D-Phe$\mathrm{NH}_3$ and $^{111}$In[DTPA-D-Phe$\mathrm{NH}_3$] octreotide (TOCT) and $^{111}$In[DTPA-D-Phe$\mathrm{NH}_3$] octreotide analogues. J Nucl Med 1992; 33: 914.


Octreotide scanning for carcinoid tumours.

M. Critchley

Postgrad Med J 1997 73: 399-402
doi: 10.1136/pgmj.73.861.399

Updated information and services can be found at:
http://pmj.bmj.com/content/73/861/399

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.

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/