New techniques in medicine

Octreotide scanning for carcinoid tumours

Mair Critchley

Summary

The somatostatin analogue octreotide may be used in the diagnosis of carcinoid and other neuroendocrine tumours. Radionuclide scanning following intravenous injection of ^{111}In -labelled octreotide (^{111}In -DTPA-pentetreotide) provides a sensitive, non-invasive method of localising somatostatin-positive tumours. The technique may also be used to identify patients who may respond to 'cold' octreotide therapy and to monitor therapeutic efficacy

Keywords: carcinoid tumours, radionuclide imaging, octreotide scanning

Figure 1 Somatostatin, octreotide, and two radiolabelled analogues of octreotide, ^{123}I -Tyr³-octreotide and ^{111}In -DTPA-pentetreotide

Department of Nuclear Medicine,
Royal Liverpool University Hospital,
Prescot Street, Liverpool L7 8XP, UK
M Critchley

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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.¹ 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.²

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'.³ 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.⁴

Somatostatin consists of 14 amino acids (figure 1) but is impracticable for radiolabelling because of its limited half-life ($T_{1/2}$ 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 octreotide⁵ 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 ($T_{1/2}$ 90–120 min) it may be labelled for radionuclide imaging.

With certain modifications, it is possible to label octreotide^{6,7} with both ^{123}I iodine (^{123}I) and ^{111}In indium (^{111}In). ^{123}I -Labelled Tyr-3 octreotide (^{123}I -

Carcinoid tumours
<ul style="list-style-type: none">• arise from neuroendocrine cells throughout the body, most frequently in 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
<p><i>¹²³I-Tyr³ octreotide</i></p> <ul style="list-style-type: none">• difficult labelling chemistry• limited availability of ¹²³I (cyclotron produced)• T_{1/2} of ¹²³I is 13 hours (not suitable for delayed imaging)• rapidly cleared via hepato-biliary system• high background tracer levels make images more difficult to interpret <p><i>¹¹¹In-DTPA-D-Phe¹-octreotide</i></p> <ul style="list-style-type: none">• easier labelling chemistry (octreotide conjugated with DTPA) enabling chelation with ¹¹¹In• T_{1/2} of ¹¹¹In is 2.8 days (suitable for delayed imaging)• clearance via renal system• low background interference easier image interpretation

Box 2

Imaging method
<ul style="list-style-type: none">• intravenous ¹¹¹In-pentetreotide: planar 111 MBq, SPECT 185 MBq• discontinue (cold) octreotide therapy three days before tracer injection

Box 3

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

octreotide) is cleared from the liver via the hepatobiliary tract into the gut with consequent inadequacy of abdominal and pelvic imaging. The relatively short half-life of ¹²³I (T_{1/2} 13 h) precludes useful delayed imaging; ¹²³I-octreotide was therefore not ideal.

¹¹¹In-LABELLED OCTREOTIDE

The development of ¹¹¹In-labelled octreotide involved the incorporation of the chelate diethylenetriaminepenta-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 T_{1/2} 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.^{8–12} 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.⁶ 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 ^{99m}Tc 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 intra-operatively.¹³ Forty-eight hours after an injection and preliminary imaging with radiolabelled octreotide, a hand-held gamma ray detection probe succeeded in

Figure 3 Abnormal octreotide scan showing carcinoid tumour of bronchus in the posterior thorax 24 h after intravenous injection of ^{111}In -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 2 cm carcinoid was removed)

Figure 4 Abnormal scan using ^{111}In -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

^{123}I -LABELLED META-IODOBENZYLGUANIDINE

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, ^{123}I -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 ^{123}I -MIBG uptake by carcinoid is 70%¹⁵ as opposed to 96% sensitivity with octreotide.⁶

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 ^{131}I . Patients imaged with ^{123}I -MIBG may proceed to treatment with ^{131}I -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 ^{111}In -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 $T_{1/2}$ such as ^{131}I ($T_{1/2}$ 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 ^{161}Tb 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

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- 1 Hammond PJ, Bloom SR, Polak JM. Hormones and the gastro-intestinal tract. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford text-book of medicine* 3rd edn. Oxford: Oxford Medical Publications, 1995; pp 1891–9.
- 2 Reubi JC. Neuropeptide receptors in health and disease; the molecular basis for in vivo imaging. *J Nucl Med* 1995; **36**: 1825–35.
- 3 Fischman AJ, Babich JW, Strauss HW. A ticket to ride: peptide radiopharmaceuticals. *J Nucl Med* 1993; **34**: 2253–63.
- 4 Krenning EP, Bakker WH, Breeman WAP, et al. Localisation of endocrine-related tumours with radiiodinated analogue of somatostatin. *Lancet* 1989; **1**: 242–5.
- 5 Kvols LK. Somatostatin-receptor imaging of human malignancies: a new era in localisation, staging and treatment of tumours. *Gastroenterology* 1993; **106**: 1909–14.
- 6 Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [^{111}In -DTPA-D-Phe] and [^{123}I -Tyr 3] octreotide. The Rotterdam experience with more than 1000 patients. *Eur J Nucl Med* 1993; **20**: 716–31.
- 7 Krenning EP, Bakker WH, Kooij PPM, et al. Somatostatin receptor scintigraphy with [^{111}In -DTPA-D-Phe]-octreotide in man: metabolism, dosimetry and comparison with [^{123}I -Tyr 3]-octreotide. *J Nucl Med* 1992; **33**: 652–8.
- 8 Kwekkeboom DJ, Krenning EP, Bakker WH, Oei HY, Kooij PPM, Lamberts SWJ. Somatostatin analogue scintigraphy in carcinoid tumours. *Eur J Nucl Med* 1993; **20**: 283–92.
- 9 Bomanji J, Mather S, Ur E, Grossman A, Besser GM, Britton KE. Imaging somatostatin receptor-positive neoplasms with [^{123}I -Tyr 3] octreotide (TOCT) and [^{111}In -DTPA-D-Phe]-octreotide (DOCT), somatostatin analogues. *J Nucl Med* 1992; **33**: 914.
- 10 Van Dongen A, Verhoeff NPLG, Bemelman F, Van Royen EA. Somatostatin receptor imaging with [^{111}In -pentetreotide for whole body studies and high resolution brain SPECT. *Eur J Nucl Med* 1992; **19**: 679.
- 11 Ivancevic V, Nauck C, Sandrock D, et al. Somatostatin receptor scintigraphy with [^{111}In] pentetreotide in gastroentero-pancreatic tumours (GEP). *Eur J Nucl Med* 1992; **19**: 736.
- 12 Olsen JO, Pozderac V, Hinkle G, et al. Somatostatin receptor imaging of neuroendocrine tumours with Indium- ^{111}Tc pentetreotide (Octreoscan). In: LM Freeman, MD Blaufox, eds. *Seminars in nuclear medicine*. Philadelphia: WB Sanders Co, 1995.
- 13 Ahlman H, Wängberg B, Tisell LE, et al. Clinical efficacy of octreotide scintigraphy in patients with midgut carcinoid tumours and evaluation of intraoperative scintillation detection. *Br J Surg* 1994; **81**: 1144–9.
- 14 Öhrvall H, Lundqvist JE, Westlin S, et al. Development of an intraoperative gamma detector probe for intraoperative use – a valuable complement to octreotide scintigraphy. *Eur J Nucl Med* 1995; **22**: 815.
- 15 Hoefnagel CA. Radionuclide therapy revisited. *Eur J Nucl Med* 1991; **18**: 408–31.
- 16 Troncone I, Galli G. Proceedings of the international workshop on the role of ^{131}I metaiodobenzylguanidine in the treatment of neural crest tumours. *J Nucl Biol Med* 1991; **35**: 177–362.
- 17 Hoefnagel CA. Metaiodobenzylguanidine and somatostatin in oncology. Role in the management of neural crest tumours. *Eur J Nucl Med* 1994; **21**: 561–81.
- 18 Taal BG, Hoefnagel CA, Valdes Olmos T, Boot H. Diagnostic imaging using ^{131}I -MIBG and [^{111}In] pentetreotide in carcinoid tumours: a key to treatment? *Eur J Nucl Med* 1995; **22**: 899.
- 19 de Jong M, Breeman WAP, Bernard BF, et al. Evaluation in vitro and in rats of ^{161}Tb -DTPA-octreotide, a somatostatin analogue with potential for intraoperative scanning and radiotherapy. *Eur J Nucl Med* 1995; **22**: 608–16.