^{111}IN-PENTETREOTIDE SCINTIGRAPHY PROCEDURE GUIDELINES FOR TUMOUR IMAGING

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Under the auspices of the Oncology Committee of the European Association of Nuclear Medicine

Key words: ^{111}In-pentetreotide scintigraphy - Tumour imaging - Procedure Guidelines - Neuroendocrine tumours - Indications

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Aim

The aim of this document is to provide general information about somatostatin receptor scintigraphy with ^{111}In-pentetreotide, a [^{111}In-DTPA-D-Phe-] conjugate of octreotide that binds to somatostatin receptors. This guideline should not be regarded as the only approach to visualise tumours expressing somatostatin receptors or as exclusive of other nuclear medicine procedures useful to obtain comparable results. It is important to remember that the resources and facilities available for patient care may vary from one country to another and from one medical institution to another. The present guide has been prepared for nuclear medicine physicians and intends to offer assistance in optimising the diagnostic information that can be obtained from ^{111}In-pentetreotide scintigraphy. The corresponding guideline of the Society of Nuclear Medicine (SNM) has been taken into consideration and partially integrated with this text. The same has been done with the most relevant literature on this topic, and the final result has been discussed by a group of distinguished experts.

Background

Somatostatin is a small, cyclic neuropeptide that is present in neurones and endocrine cells; it has a high density in the brain, peripheral neurones, endocrine pancreas and gastrointestinal tract. Naturally occurring somatostatin has a very short plasma half-life (1-3 min) and therefore synthetic analogues have been developed, including octreotide acetate. In the ^{111}In-pentetreotide molecule, the biologically active ring of octreotide remains intact and a DTPA bridge is coupled to the phenylalanine group so that it can be labelled with ^{111}In. ^{111}In-labelled pentetreotide specifically binds to somatostatin receptors, with particular affinity to subtypes 2 and 5. Somatostatin receptors have been identified on many cells of neuroendocrine origin; additionally, several non-neural and non-endocrine cells sometimes display somatostatin receptors with various degrees of density. Consequently, tumours deriving from cell types expressing somatostatin receptors may be imaged by somatostatin receptor scintigraphy.

Disease processes that may be visualised by somatostatin receptor scintigraphy include the following:

<u>Neuroendocrine tumours</u>

- sympathoadrenal system tumours (phaeochromocytoma, neuroblastoma, ganglioneuroma and paraganglioma)
- functioning and non-functioning gastroenteropancreatic tumours (GEP) (carcinoid, gastrinoma, insulinoma, glucagonoma, VIPoma, etc.)
- medullary thyroid carcinoma
- pituitary adenoma
- Merkel cell carcinoma
- small cell lung cancer

<u>Other tumours</u>

- breast carcinoma
- melanoma
- lymphomas
- prostate carcinoma
- non-small cell lung cancer
- sarcoma
- renal cell carcinoma
- differentiated thyroid carcinoma
- astrocytoma
- meningioma

<u>Non-neoplastic diseases</u>

- autoimmune diseases
- granulomas
- thyroid associated ophtalmopathy
- post-radiation inflammatory disease
- bacterial infections.

Clinical indications

The main indication for ^{111}In-pentetreotide scintigraphy is the imaging of neuroendocrine tumours such as GEP tumours and sympathoadrenal system tumours, which usually display a high density of somatostatin receptors. Imaging of somatostatin receptors in non-neuroendocrine tumours is not included in the current diagnostic routine but may be useful especially for planning radiotherapeutic treatment with radiolabelled somatostatin analogues.

In the management of patients with neuroendocrine tumours ^{111}In-pentetreotide scintigraphy can be used to:

- localise primary tumours and detect sites of metastatic disease (staging and restaging);
- detect relapse or progression of disease (follow-up of patients with known disease);
- monitor the effects of surgery, radiotherapy or chemotherapy;
- predict the response to therapy as a prognostic parameter;
- select patients for peptide receptor radionuclide therapy.

Since the density of somatostatin receptors on neuroendocrine tumours may vary, the sensitivity of ^{111}In-pentetreotide is likely to vary among tumour types. The sensitivity of ^{111}In-pentetreotide scintigraphy may be reduced in patients who are receiving therapeutic doses of octreotide acetate. For these reasons ^{111}In-pentetreotide scintigraphy cannot be considered as the first-choice nuclear medicine modality in the management of patients with non-neuroendocrine tumours, except for the determination of somatostatin receptor status.

Precautions

- Pregnancy (suspected or confirmed). In the case of a diagnostic procedure in a patient who is known or suspected to be pregnant, a clinical decision is necessary to consider the benefits against the possible harm of carrying out any procedure.
- Breastfeeding. If radiopharmaceutical administration is considered necessary, breastfeeding should be interrupted and can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1 mSv.
- The potential hazard of ionising radiation from ^{111}In-pentetreotide administration must be carefully evaluated in subjects under 18 years of age.
- In patients with significant renal failure administration of ^{111}In-pentetreotide is not recommended because the impairment of the principal route of excretion will lead to delivery of an increased radiation dose. Interpretable scintigrams may be obtained after haemodialysis. Prior to dialysis images are non-diagnostic because of activity in the circulation. After dialysis a higher than usual uptake in liver, spleen and intestinal tract and a higher than usual activity in the circulation have been observed.
- It is recommended to temporarily withdraw somatostatin analogue therapy (when possible) to avoid possible somatostatin receptor blockade (see patient preparation). In some patients the withdrawal of therapy might not be tolerated. This is notably the case in insulinoma patients, where the danger of sudden hypoglycaemia must be considered, and in patients suffering from the carcinoid syndrome.
- In diabetic patients receiving high doses of insulin the administration of pentetreotide may cause paradoxical hypoglycaemia via a temporary inhibition of glucagon secretion.

Pre-examination procedures

1) Patient preparation

- The technologist or physician should give the patient a thorough explanation of the test.
- It is recommended to temporarily withdraw somatostatin analogue therapy (when possible and not contraindicated) to avoid possible somatostatin receptor blockade. The time interval between interruption of therapy and administration of ^{111}In-pentetreotide depends on the type of drugs used. At least one day is suggested for short-lived molecules and 3-4 weeks for long-acting formulations.
- Although only 2% of the administered dose undergoes hepatobiliary excretion, it is necessary to minimise the potential for visualising artefacts in the intestine when abdominal lesions are suspected. It is advised to administer a laxative, especially when the abdomen is the area of interest. A mild oral laxative should be administered on the day before injection and continued

throughout the day(s) of imaging. In patients with insulinomas bowel cleansing must not be undertaken without consulting the endocrinologist in charge of the patient.
- Ample fluid intake is necessary to reduce the radiation exposure. Patients must be well hydrated before and at least 1 day after injection.

2) Pre-injection

All information useful for a better interpretation of somatostatin receptor scintigraphy should be considered by the nuclear medicine physician:
- relevant history of suspected or known primary tumour
- absence or presence of functional symptoms
- laboratory test results (circulating hormones, tumour markers)
- results of any other imaging studies (CT, MRI, US, X-rays)
- history of recent biopsy, surgery, chemotherapy, radiation therapy
- history of recent somatostatin analogues therapy.

3) ^{111}In-pentetreotide injection, administered activity

- ^{111}In-pentetreotide is commercially available as OctreoScan. The radiopharmaceutical should be administered using an indwelling catheter or butterfly needle, thus avoiding paravasal deposition of activity.
- The activity of radiopharmaceutical to be administered should be determined after taking account of the European Atomic Energy Community Treaty, and in particular article 31, which has been adopted by the Council of the European Union (Directive 97/43/EURATOM). This Directive supplements Directive 96/29/EURATOM and guarantees health protection of individuals with respect to the dangers of ionising radiation in the context of medical exposures. According to this Directive, Member States are required to bring into force such regulations as may be necessary to comply with the Directive. One of the criteria is the designation of Diagnostic Reference Levels (DRL) for radiopharmaceuticals; these are defined as *levels of activity for groups of standard-sized patients and for broadly defined types of equipment.* It is expected that these levels will not to be exceeded for standard procedures when good and normal practice regarding diagnostic and technical performance is applied. For the aforementioned reasons the following activity for ^{111}In-pentetreotide should be considered only as a general indication, based on literature data and current experience. However, it should be noted that in each country nuclear medicine physicians should respect the DRLs and the rules stated by the local law. Activities higher than the DRLs must be justified.
- The activity reported in the literature ranges from 120 to 220 MBq (3.2-5.9 mCi), mean activity 175 MBq (4.7 mCi). The recommended activity to obtain a good imaging quality is about 200 MBq (5.4 mCi). The experience in paediatric patients is very limited; when the use of the radiopharmaceutical is considered necessary in a child the activity should be reduced according to the recommendations of the EANM Paediatric Task Group. The organ which receive the largest radiation dose is spleen followed by kidneys and bladder (see Table).
- The amount of pentetreotide injected is at least 10 µg; this amount is not expected to have any clinically significant pharmacological effect. The *in vitro* biological activity of ^{111}In-pentetreotide is approximately 30% of the biological activity of natural somatostatin. Intravenous administration of 20 µg of pentetreotide resulted in some patients in a measurable but very limited decrease in serum gastrin and serum glucagon levels of less than 24 hours' duration.^{111}In-pentetreotide should not be injected into intravenous lines together with solutions for parenteral nutrition.

4) Post-injection

Patients should void before scanning. Abundant fluid intake is required for 2 or 3 days following administration. Elimination of the extra fluid intake will help to flush out unbound labelled pentetreotide and non-peptide-bound ^{111}In by glomerular filtration. This will reduce the background noise as well as the radiation dose to kidneys and bladder.

Physiological ^{111}In-pentetreotide distribution

^{111}In-pentetreotide is rapidly cleared from the blood: 35% of the injected activity remains in the blood pool at 10 minutes and only 1% at 20 hours after injection. Excretion is almost entirely through the kidneys: approximately 50% of the intravenously administered activity is found in the urine by 6 hours and 85% within 24 hours. Hepatobiliary excretion and elimination via the faeces account only for 2% of the total administered activity.

Somatostatin receptors are expressed by many neuroendocrine and non-neuroendocrine cells of the body, so different organs may be imaged by somatostatin receptor scintigraphy including the liver (approx. 2% at 24 hours), spleen (approx. 2.5% at 24 hours), pituitary, thyroid, and kidneys. Stimulated adrenal glands may be faintly visualised. Other organs are shown at different times as a result of the clearance of ^{111}In-pentetreotide: gallbladder, bowel, renal collecting system, ureters and bladder.

Radiation dosimetry

The estimated absorbed radiation dose to various organs in healthy subjects following administration of ^{111}In labelled-octreotide is given in the Table. The data are quoted from ICRP No. 80.

	Absorbed dose per unit activity administered (mGy/MBq)		
Organ	Adult	15 years	5 years
Adrenals	0.058	0.075	0.17
Bladder	0.20	0.25	0.46
Bone surfaces	0.027	0.034	0.076
Brain	0.0096	0.012	0.033
Breast	0.012	0.015	0.037
Gall bladder	0.052	0.063	0.14
Stomach	0.043	0.050	0.11
Colon	0.029	0.036	0.089
Heart	0.025	0.032	0.071
Kidneys	0.41	0.49	0.96
Liver	0.10	0.13	0.27
Lungs	0.023	0.030	0.068
Muscles	0.020	0.026	0.057
Oesophagus	0.014	0.019	0.044
Ovaries	0.027	0.035	0.081
Pancreas	0.072	0.088	0.20
Red marrow	0.022	0.027	0.053
Spleen	0.57	0.79	1.8
Testes	0.017	0.023	0.055
Thymus	0.014	0.019	0.044
Thyroid	0.076	0.12	0.37
Uterus	0.039	0.049	0.11
Effective dose (mSv/MBq)	**0.054**	**0.071**	**0.16**

Radiopharmaceutical: [^{111}In]pentetreotide

Description

^{111}In-labelled pentetreotide is commercially available as OctreoScan®. It is supplied, as two vials:

Vial A: ^{111}In as $InCl_3$, 122 MBq (3.3 mCi)/1.1 ml at ART

Vial B: 10 µg of lyophilised pentetreotide and excipients

Preparation

The contents of vial A are added to vial B according to the manufacturer's instructions. After reconstitution and labelling the solution contains ^{111}In-pentetreotide in trisodium citrate, citric acid, inositol, gentisic acid, ferric chloride and hydrochloric acid; 0.02 N. After reconstitution and labelling the pH of the aqueous solution is 3.8-4.3

Quality control

The radioactive concentration should be determined by measuring the activity of the vial in a calibrated ionisation chamber. Radiochemical purity may be confirmed using a TLC method. (Solid-phase ITLC, mobile-phase 0.1N sodium citrate adjusted with HCl to pH 5, Rf: ^{111}In-pentetreotide 0.0, unbound indium-111 1.0). Labelling efficiency should be >95%.

Special precautions

The preparation may be diluted with 2-3 ml of sterile physiological saline if required.

Gamma camera quality control

A strict quality control programme should be routinely performed according to the rules of each country, as stated in the Council Directives97/43/ EURATOM.

Image acquisition

1) Instrumentation

Gamma camera fitted with a medium-energy, parallel-hole collimator.

Energy window: ^{111}In photopeaks (172 and 245 keV) with 20% windows summed in the acquisition frames.

A large-field-of-view gamma camera is required for total body imaging.

2 Acquisition modality

- Planar and SPECT images should be acquired at 4 and 24 hours or 24 and 48 hours post-injection. It is important to acquire two sets of images, with at least one SPECT acquisition. Spot views may be repeated at 48 hours, 72 hours, and/or 96 hours p.i. to allow clearance of interfering bowel radioactivity.
- Planar images: Both anterior and posterior of head, neck, chest, abdomen, pelvis and lower extremities. 15 min counts per view, 256x256 matrix. Right and left lateral views may be added for head and neck images.
- Whole body: Maximum scanning speed of 3 cm per minute. A whole-body image may substitute for anterior and posterior spot images of head/neck/chest/abdomen, however with lower sensitivity to detect lesions.
- SPECT: degrees of rotation: 360; number of projections: 60; time per projection: at least 45 seconds; acquisition matrix: 64x64 word.

Planar and SPECT studies are preferably performed 24 hours after injection of the radiopharmaceutical. Scintigraphic studies after both 24 and 48 hours can be carried out with the same protocol. Repeat scintigraphy after 48 hours is especially indicated when 24-hour scintigraphy shows accumulation in the abdomen, which may also represent radioactive bowel content.

Optional images

Four-hour images have a relatively high background radioactivity, but have the advantage of negligible bowel activity. High background radioactivity may have the effect of missing lesions, expressing a rather low density of somatostatin receptors.

Image processing

SPECT data are usually prefiltered using a low-pass filter. The order and frequency are chosen according to the preference of individual centres and recommendations of the software manufacturer. The data are reconstructed using a ramp filter and attenuation correction. Iterative reconstruction algorithms, when available, may eliminate artefacts.

Imaging analysis

Abnormal uptakes should be visually evaluated by a nuclear medicine physician.

Some authors have proposed scoring of the visual uptake on a five-point scale: 0, no uptake; 1, very low/equivocal uptake; 2, clear but faint uptake (less than or equal to liver uptake); 3, moderate uptake (higher than liver uptake); 4 intense uptake. This can help in defining the lesion's avidity and in comparing uptake differences in the course of serial evaluations.

Interpretation criteria

To evaluate somatostatin receptor scintigraphy images, the following items should be taken into consideration:

- clinical issue raised in the request for ^{111}In-pentetreotide imaging
- clinical history of the patient
- knowledge of normal tissue accumulation and timing (e.g. intestinal activity is absent at 4 hours but present at 24 hours)
- anatomical localisation of the uptake according to other non-nuclear medicine imaging data
- intensity of the ^{111}In-pentetreotide uptake
- semiquantitative value (if available)
- clinical correlation with any other data from previous relevant clinical, biochemical and morphological examinations
- comparison between early and late images
- sensitivity of ^{111}In-pentetreotide scintigraphy in detecting different tumour types, which is related to tumour histology, expression and density of somatostatin receptors and site of the lesion(s)
- the sensitivity in detecting lesions with limited uptake is better in most cases with static rather than whole-body images
- causes of false negative results
- causes of false positive results.

Reporting

The nuclear medicine physician should record all information regarding the patient, a concise patient history, type of examination, date, radiopharmaceutical (administered activity and route), relevant medications (patient preparation, octreotide therapy, withdrawal, chemotherapy, etc.), laboratory results, all data obtained by other imaging studies, and the clinical question.

The report to the referring physician should describe:

1) the procedure (^{111}In-pentetreotide activity administered, timing of imaging, area imaged, SPECT performed, etc.);
2) findings (site of the lesion(s), uptake intensity, etc.);
3) comparative data (the findings should be related to previous information or results of other clinical or instrumental examinations);
4) interpretation: a clear diagnosis should be made if possible, accompanied - when appropriate - by a description of the study limitations (potential causes of false negative or false positive results). In case the conclusive impression should require additional diagnostic examinations or an adequate follow-up, this must be recommended.

Sources of error

- The pituitary and the thyroid are faintly visible. Intense accumulation of radioactivity is seen in the spleen and kidneys. Accumulation in the liver can be compared to the intensity of the spleen.
- Radioactivity is almost always found in the bowel on the 24-hour image. Caution must be used to avoid interpreting physiological colon activity as intestinal lesions. Radioactivity in the bowel on the 24-hour image is most often localised within the colon, from the caecum to the rectum. On the 48-hour image the signal is differently distributed or even gone upon laxation.
- On the 24-hour image the gallbladder is often visible. The gallbladder is always visible on SPECT images, even if it is not visible on the planar image due to overprojection of the kidney and liver. Caution must be used since normal gallbladder activity may sometimes be confused with liver metastases.
- Patients with respiratory infections often show accumulation in the nasopharynx, and to alesser extent in trachea and pulmonary hilar areas, most probably due to radiopharmaceutical accumulation in the lymphocytes.
- Diffuse pulmonary or pleural accumulation can be observed after radiation therapy to the thoracic area or following bleomycin therapy. Patients on somatostatin analogue therapy can be recognised by reduced uptake in the spleen.

- The tracer may accumulate in areas of recent surgery and at colostomy sites.
- Contamination with urine of clothes and/or skin may cause false positive images.
- Octreotide therapy or the endogenous production of somatostatin (by the tumour) may reduce tumour detectability.
- Variable tumour differentiation and heterogeneous expression of somatostatin receptor subtypes may influence the affinity for ^{111}In-pentetreotide and thereby tumour detectability.
- Liver metastases from neuroendocrine tumours are sometimes not seen because receptor expression by the tumour is isointense to that of normal liver cells.
- Women sometimes show slight tracer uptake in the breast region; such physiological uptake is symmetrical.
- It should be remembered that positive scintigraphy with ^{111}In-pentetreotide reflects the presence of an increased density of somatostatin receptors rather than malignant disease. Uptake is not specific for tumours. Positive scintigraphic results require evaluation of the possibility that other disease characterised by high local somatostatin receptor concentrations may be present. The intensity at which pathological processes are visible may vary considerably.

Issues requiring further clarification

- Many non-neuroendocrine tumours express somatostatin receptors and can thus be visualised using somatostatin receptor imaging (e.g. breast cancer, lymphomas, meningiomas, astrocytomas, renal cell carcinoma, etc.). The role of ^{111}In-labelled pentetreotide scanning in patients with these tumours has not been clearly demonstrated and should be further investigated.
- The density of somatostatin receptors has been studied as a marker of aggressiveness of some neuroendocrine and non-neuroendocrine tumours. A semiquantitative evaluation *in vivo* of ^{111}In-pentetreotide uptake using SPECT images has been proposed as a prognostic parameter in neuroblastoma and GEP tumours. The clinical usefulness of this approach has to be further evaluated.
- Other radiolabelled somatostatin analogues or radiopharmaceuticals for tumours expressing somatostatin receptors are available, under study or about to be available. Among these, also radiopharmaceuticals for PET can be used. Even if ^{18}F-FDG has been successfully and widely employed in oncology, it has not demonstrated a satisfactory uptake in well differentiated neuroendocrine tissues. On the contrary other positron emitter tracers seem to be more promising. Accurate cost-benefit analysis of the many options in this area is required.
- Little is known about the ^{111}In-pentetreotide elimination in patients with impaired renal function. Dose adjustment in these patients is a topic for further studies.

Disclaimer

The European Association has written and approved guidelines to promote the use of nuclear medicine procedures with high quality. These general recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures and exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialised practice setting may be different than the spectrum usually seen in a more general setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, resource available for patient care may vary greatly from one European country or one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Acknowledgements: the Authors thanks Ms. Annaluisa De Simone Sorrentino and Ms. Marije de Jager for their valuable editorial assistance.

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Guidelines issued date: September 2, 2003