OVERVIEW: Neuroendocrine Tumor Imaging

Users of this tutorial will learn how to name the three radiopharmaceuticals suitable for use in detection of neuroendocrine tumors and their required storage conditions; will be able to list the most common indications for ordering this test; will be able to state the prescribed injected dose for each; will be able to describe patient preparation and thyroid blockage (as required) for each of these drugs; will be able to state the time and imaging parameters for planar and SPECT imaging; will be able to identify the sites of localization of each drug in a normal patient and will be able to identify neuroendocrine tumors on scans typical of the disease.

Radiopharmaceuticals Utilized in Neuroendocrine Tumor Imaging

- I-123 mIBG and I-131 mIBG
- In-111-Octreoscan (In=111-Pentetreotide)

Imaging of neuroendocrine tumors with I-123 mIBG and I-131 mIBG

INDICATIONS FOR CLINICAL STUDIES

- Pheochromocytoma
- Neuroblastoma
- Paraganglioma
- Medullary carcinoma of the thyroid
- Carcinoid tumors
- Medullary hyperplasia of adrenals
EPIDEMIOLOGY

- 0.1-0.5% of all hypertensives have a pheochromocytoma
- Occurs in both sexes at all ages. The younger the patient, the more likely the disease is familial
- Neuroblastoma is the second leading cause of death in children due to cancer
- Epidemiology
- Family history of certain syndromes associated with high incidence of pheochromocytoma, e.g., Neurofibromatosis, Multiple Endocrine Neuroplasia Syndrome (MEN), Von-Hipple Lindau disease

DIAGNOSTIC PATTERNS

- Family History
- Symptoms
- Clinical Data, for example
- Sustained or labile hypertension, unusually severe, markedly labile spells
- Hypertension plus spells (include sweating, palpitations, headache)

THE 10% RULE FOR PHEOCHROMOCYTOMAS

- 10% Multiple
- 10% Extra Adrenal
- 10% Bilateral
- 10% Familial
- 10% Malignant

PROCEDURES THAT EXPLORE ANATOMICAL SITES

- Computed Tomography and MRI
- Ultrasound
- Scintigraphy with *I-mIBG or 111In Octreoscan
- Arteriogram guided by norepinephrine level
- Norepinephrine levels from different sites of vena cava
DRUG AVAILABILITY
I-123 mIBG: NDA Approved; available in US as of December 2008
I-131 mIBG: NDA Approved; available in US as of June, 1994

*I-mIBG STRUCTURE

CHARACTERISTICS OF I-123 and I-131

- $t_{\text{phys}}$ of I-123 = 13.3 hr; $E_{\gamma} = 159$ keV
- $t_{\text{phys}}$ of I-131 = 8.08 days; $E_{\gamma} = 364.5$ keV

PATIENT PREPARATION FOR I-mIBG INJECTION

- Thyroid Blockage with SSKI
- For I-123 mIBG, ten drops at least 30 minutes prior to injection of mIBG and three drops once a day for three days
- For I-131 mIBG, ten drops at least 30 minutes prior to the scan and three drops once a day for ten days
- Patient must drink extra fluid for 24 hr post injection to minimize radiation dose to urinary bladder and gonads

TYPICAL ADMINISTERED DOSE FOR ADULTS

- For I-123 -mIBG: 5-10 mCi
- For I-131-mIBG: 0.5 mCi
DRUG ADMINISTRATION PROCEDURE

- Inject over a two minute period
- Use a saline flush to keep butterfly open
- Observe patient for 20 min post injection to insure adverse reaction has not occurred
- Release patient

IMAGING TIMES

- For I-123 mIBG: whole body scan and posterior abdominal view at 24 hr post injection; posterior abdominal view at 36-40 hr post injection
- For I-131 mIBG: whole body scan and posterior abdominal view at 48 hr post injection; posterior abdominal view at 72 hr post injection

ADVERSE REACTIONS FOLLOWING IV INJECTION OF *I-mIBG

At our university, we have injected >1,000 patients with no recorded adverse reactions

CONTRAINDICATIONS: DRUGS THAT BLOCK UPTAKE OF mIBG

- Cocaine
- Reserpine Alkaloids
- Labetalol
- Phenylpropanolamine
- Tricyclic Antidepressants

NORMAL DISTRIBUTION OF *I-mIBG

- Myocardium
- Uptake is inversely proportional to circulating catecholamine levels
- Liver
- Adrenals
- Salivary glands
- Bowel (occasionally)
RADIATION DOSIMETRY OF I-131 -mIBG

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>RADS / 0.5 mCi</th>
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<tbody>
<tr>
<td>Adrenal Cortex</td>
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<tr>
<td>Adrenal Medulla</td>
<td>69.0</td>
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<tr>
<td>Kidneys</td>
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<tr>
<td>Liver</td>
<td>0.2</td>
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<tr>
<td>Ovaries and Testes</td>
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<tr>
<td>Pancreas</td>
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<tr>
<td>Spleen</td>
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<td>Thyroid-Unblocked</td>
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<tr>
<td>Thyroid- Blocked</td>
<td>&lt;1.0</td>
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<tr>
<td>Whole Body</td>
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</table>

Clinical Cases: Neuroendocrine Tumor Imaging with I-123 mIBG and I-131 I mIBG

Conclusions

- Image quality of I-123 mIBG is superior to that obtained using I-131 mIBG
- Image time significantly reduced with I-123
- Sensitivity and specificity are both >90%

Clinical Study # 1: Patient WW

- 55 y/o WM, right adrenal mass on MRI
- history of HTN X 15 yr
- thyroid blocked with SSKI solution
- injected with 0.5 mCi of I-131 mIBG
Clinical Study # 2: Patient EF

■ 44 y/o BF
■ History of HTN, anxiety
■ thyroid blocked with SSKI solution
■ injected with 10.5 mCi of I-123 mIBG

Clinical Study # 3: Patient SA

- thyroid blocked with KClO4
- 16y/o obese WF, R adrenal mass on CT
- history of HTN X several months
- elevated urinary catecholamines
- Medication: dibenzylene, 10 mg q 6 hr
- injected with 8.5 mCi of I-123 mIBG

Clinical Study # 4: Patient MR

- 35 Y/O WM
- History of difficult-to-control HTN
- Mass seen on CT
- thyroid blocked with SSKI solution
- injected with 9.8 mCi of I-123 mIBG
Clinical Study # 5: Patient KT

- 60 y/o WF
- History of pheochromocytoma 8 years prior to this study.
- Has recurrence of HTN and other symptoms
- Medication: beta blockers
- Thyroid blocked with SSKI solution
- Injected with 10 mCi of I-123 mIBG
IMAGING OF NEUROENDOCRINE TUMORS: In-111 Octreotide

PATIENT INDICATIONS

- In-111 Octreotide is indicated for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors.

TUMOR TYPES IMAGED

- Neuroblastomas
- Pheochromocytomas
- Paraganglioma
- Carcinoid Tumors
- Medullary Thyroid Ca
- VIPoma
- Insulinomas
- Gastrinomas
- Pituitary Adenoma
- Glucagonoma
- Islet Cell Carcinomas
- Small Cell Lung Ca

CHARACTERISTICS OF In-111

- \( t_{\text{phys}} = 2.805 \text{ d} = 67.32 \text{ hr} \)
- 171.3 keV gamma: 90.2 % abundance
- 245.4 keV gamma: 94.0 % abundance

RADIOTRACER USED

- 3-6 mCi of high purity In-111 trichloride in dilute HCl in a 10 ml vial

RADIOCHEMICAL REACTION

- \( \text{In}^{3+} + \text{DTPA-Octreotide} \rightarrow \text{In-DTPA-octreotide} \quad \text{final pH: 3.8-4.3} \)
BASIC LABELING THEORY

- DTPA group is covalently bonded to Octreotide molecule. In-111 actually bonds to DTPA portion of molecule, not to octreotide

MOLECULAR STRUCTURE OF OCTREOTIDE

PATIENT PREPARATION

- Patient must be very well hydrated before the dose and for up to 48 hr afterward to minimize internal radiation dose
- Patient must take a mild laxative the evening before administration of the drug and continue for 2 days.

ADMINISTERED DOSE

- For Planar/pediatric imaging: 3 mCi = 111 MBq
- For SPECT imaging: 6 mCi = 222 MBq
- Must perform visual inspection to insure absence of particulates

CONTRAINDICATIONS

- Sensitivity to somatostatin and its analogues
ADVERSE REACTIONS OCCURRING IN <1% OF ALL PATIENTS

- dizziness
- fever
- flushing
- headache
- hypotension
- increased liver enzymes
- joint pain
- nausea
- sweating
- weakness

ADVERSE REACTIONS OCCURRING IN <3% OF ALL PATIENTS

- diarrhea and vomiting
- abdominal
- pain/discomfort
- injection site pain

CLINICAL PHARMACOLOGY

- Pentetreotide is a long acting analog of the hormone somatostatin
- Initially concentrates in plasma.
- The In-111 complex binds avidly to somatostatin receptors throughout the body.
- Within 1 hr, most of the In-111 octreotide distributes to extravascular body tissues and in tumors containing a high density of somatostatin receptors.
- After background clearance via the kidneys, visualization of somatostatin rich receptors is achieved.
- t₁/₂ of clearance from blood is 7-8 min
- By 20 hr post injection, <1% of In-111 activity remains in blood.
- Whole body biological half-life of In-111 Octreotide is 6 hr
NORMAL DISTRIBUTION OF In-111-Octreoscan

- Normal pituitary gland
- thyroid gland
- liver
- spleen
- kidneys
- urinary bladder
- bowel (occasionally)

INTERNAL RADIATION DOSIMETRY

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>RADS / 6 mCi</th>
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<td>KIDNEYS</td>
<td>10.8</td>
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<tr>
<td>LIVER</td>
<td>2.4</td>
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<tr>
<td>SPLEEN</td>
<td>14.8</td>
</tr>
<tr>
<td>BONE MARROW</td>
<td>0.7</td>
</tr>
<tr>
<td>BLADDER WALL</td>
<td>6.1</td>
</tr>
<tr>
<td>STOMACH WALL</td>
<td>1.1</td>
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<tr>
<td>UPPER GI</td>
<td>1.2</td>
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<tr>
<td>LOWER GI</td>
<td>1.6</td>
</tr>
<tr>
<td>ADRENALS</td>
<td>1.5</td>
</tr>
<tr>
<td>THYROID</td>
<td>1.5</td>
</tr>
</tbody>
</table>

CLINICAL IMPACT OF OCTREOSCAN IMAGING

- Yielded information about localizations not previously identified: 27.9% (57/104)
- Demonstrated uptake in lesions known to exist, but not verified as neuroendocrine tumors 28.2% (55/195)
- Localized neuroendocrine tumors in patients with clinical and hormonal evidence of tumor, but no prior localizations 37.5% (21/56)
- Produced a change in patient management-31.1% (64/206)