NUCLEAR MEDICINE

clinical molecular imaging + endo-radiotherapy

INTRODUCTION

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DEFINITION OF NUCLEAR MEDICINE

Medical applications of unsealed radioisotopes for
Diagnosis – Therapy - Research
„Unsealed”: into the living organism, functions
iv., sc., per os, inhalation, etc.
Participation in organ-tissue-molecular functions!
(Not the brachytherapy. In vitro diagnostic use??)

Independent medical specialty (5 yr specialization)
Diagnosis + Therapy of diseases (not only imaging!)

HEVESY GYÖRGY
Georg von Hevesy

Isotopes:
same chemical (and biochemical) characteristics, no biological differences
First use in biological systems (1924)
Tracer principle: to follow the functions
small amount, same biochem.
but radioactive (detection)
„Father of nuclear medicine”
Nobel prize in chemistry 1943

RADIOISOTOPES IN MEDICINE

Isotope: the same number of protons
(same place in the periodic sytem)
chemically the same element!
(e.g. C-11, O-15, I-123-124-125-127-131)
biochemically: no difference!
Proton : neutron. Optimal ratio: stability !
Unstable nucleus changes: radiations
Two types of isotopes :
plus protons or plus neutrons
Production (only arteficial isotopes are used):
plus proton: in cyclotron
plus neutron: in reactor

TYPE OF RADIATION

Plus protons:

- positron emission (positive beta particle)
  meets an electron : annihilation
  2 x 511 keV electromagnetic radiation
- EC (K, L, M...): „avalanche”
  characteristic Xray+gamma emission
- alpha particle (large!)

Plus neutrons:

beta (negative) „electron” from the nucleus
+ gamma (immediately or metastable)

IMPORTANT RADIONUCLIDES (NM)

Diagnostic: electromagnetic radiation (photons)

plus neutron:

Tc-99m, I-131, Xe-133: gamma radiation

plus proton:

- Ga-67, In-111, I-123, Tl-201: Xray +gamma
- C-11, N-13, O-15, F-18, Ga-68: annihilation

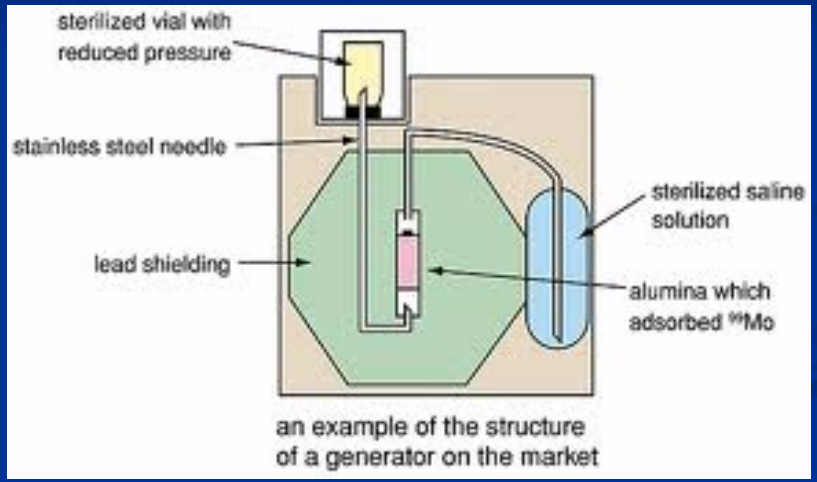
Therapeutic: particle (absorption in tissue: dosis)

plus neutron: beta: Y-90, I-131, Sm-153, Re-186,..

plus proton: alpha - At-211, Bi-212, Ra-223, ..

Tc-99m GENERATOR

Mo-99 on Al-oxid, elution with physiologic NaCl
physical half life T1/2: 2.75 day



an example of the structure of a generator on the market

ADVANTAGES OF Tc-99m

(m=metastable: gamma radiation slowly)
In 80 % of SPECT examinations

Physical (for detection)

140 keV: ideal for gamma camera (70-400 keV)
monoenergetic: ideal for imaging

Biologic: low radiation dose

(high amount of activity, high number of photons)
”pure” gamma from Mo-99: without beta
physical T1/2: 6 hours is optimal

Practical

from Mo-99-generator , elution with phys. saline
stable complexes with many molecules

SPECT: MAINLY WITH TC-99m
When NOT Tc-99m ?

1. If not possible to label with Tc-99m
   e.g. glucose, small molecules

2. Too slow is the function (biokinetics)
   e.g. steroid hormon synthesis

RADIOPHARMACEUTICALS

Organ- tissue- molecular-
function-specific labeled molecules
(only the isotope: e.g. I-131, Rb-82, Ra-223)

Diagnosis:
Functions: organ, tissue, molecular functions
Tissue characterization – identification
Quantification

Therapy:
targeted, molecular (selective) endo-radiotherapy
high dose, because continous radiation
„tailored", „personalized"

Role of radioisotope is: only for detection or for therapy

BIOLOGICAL MECHANISM
for uptake of radiopharmaceuticals

Physical	SLN
Compartment	MUGA blood pool
Diffusion	DTPA, ventilation
Chemical reaction	MDP, PIB
Phagocytosis	colloid spleen
Cells	leucocyte
Excretion	HIDA, EC
MOLECULAR TARGETS:	
Active transport	***thyroid (NIS), adrenerg (NET)***
Metabolic-enzymes	***FDG, FET, FCH, FLT,..***
Antigen	***antibody, fragment, peptides***
Receptor	***ligand***
Beta-amyloid	***florbetapir***
Others	***hypoxia, angiogenesis, etc.***

THERANOSTICS CONCEPT

Molecules are specific!

The same molecule!

Role of radioisotope:

only for detection or for therapy

Image-based targeted endo-radiotherapy!

e.g.	Radioiod:	I- 123 -124 -125 -131
	SMS analogues:	In-111, Tc-99m, Ga-68, Y-90, Lu-177, Bi-213,
	PSMA	Ga-68 – Lu-177

IMAGING INSTRUMENTS

Gamma camera

scintillation crystal, rectangular detectors, FOV
static and dynamic aquisitions mode
spot, whole-body images
planar or SPECT: many projections and reconstruction
ECG-gated aquisition
dedicated cameras (for organs e.g.: thyroid, heart)
multipinhole, small animal SPECT…)
corrections (attenuation, Compton, resolution recovery)

Positron camera: PET („double-photon emisson CT")

crystals: BGO, GSO, LSO, LYSO,…
ring detectors (many small block detectors)
16-26 cm axial FOV
coincidence detection, 3D data aquisition

DETECTION: NON-IMAGING

Ex vivo measurements of biological samples

e.g. renal clearance (blood),
Schilling test (urine)

Small dedicated non-imaging instruments

Thyroid uptake test: single gamma-probe
radioiodide therapy, activity calculation
Intraoperative gamma-probe for localization
e.g. sentinel lymph node detection

PET vs. SPECT

Advantages of PET

1. Much more sensitive (no collimator!)
2. Spatial resolution is better (anatomic details)
   SPECT: 10 mm, PET: 4 - 5 mm (FWHM)
   (small animal: even 1 mm!!)
3. Quantitation is easier
   (not only relative, in %, e.g. lung, kidney)
   but absolute as well (e.g. mL/min/g, mol/min/g)
4. **<u>Biomolecules can be labeled !!!</u>**
   C-11, N-13, O-15, F-18, I-124, Ga-68, …
   (glucose, tyrosine, thymidine, H2O, etc…..)

PET: SLICES OF LIFE

HYBRID SYSTEMS

Function + Morphology
on the same gantry: „simultaneous" (image fusion?)
Improvement of diagnostic capabilities
1 +1 = 3 !

PET/CT (today only hybrid is produced)
SPECT/CT also („good" SPECT= SPECT/CT)
role of CT: localization + attenuation correction
„low dose" ! (not diagnostic CT!)
PET/MR
no radiation (pediatry, brain, oncology, …?)

PET/MR

Development of detector technology

PET (photomultipliers?) in magnetic field!

MR: 1. Soft-tissue contrast excellent

head and neck, pelvis, brain

2. No radiation dose!

pediatric patients, follow-up studies

Attenuation correction ?

Duration of the study (MRI is longer, sequences?)

Clinical indications: work in progress

Excellent for biomedical research !

Cost-effectiveness ???

ADVANTAGES OF NM IN DIAGNOSIS

Tissue characterization - identification

What is seen on the CT/MRI?

Functions!

Organ- Tissue- Cell- Molecular Functions

Quantitative e.g. renal: split, MTT, clearance

thyroid uptake, I-131 %

heart perfusion score

PET: SUV, or mmol/min/g

Non-invasive

i.v. injection and (small) radiation dose

No toxic effects! Allergic reactions very rare.

Nano-, picomolar amount of substances

DISADVANTAGES OF NM - I.

1. Geometric resolution is limited

contrast is seen (target/backgoround ratio)

like stars on the sky (light!!! but size??)

only the function!

technical resolution

SPECT 10 mm, PET 4 mm (FWHM)

biologic resolution is different!

hot thyroid nodule! but mets in large liver?

2. Anatomy, localization ?

hybid instruments help

SPECT/CT, PET/CT, PET/MR, (SPECT/MR?)

DISADVANTAGES OF NM - II.

3. Radiation dose (risk-benefit?)

Gamma	1- 7 mSv
Annihilation (PET)	5-10 mSv
EC, conversion e.	15 mSv

Principles of radioprotection

Indication!

Non-ionizing!

ALARA !

only diagnostic reference levels

Developments of instrum. (hardware, software)

Gravidity, lactation, small children !?!

ROLE OF NM and RADIOLOGY in diagnostic imaging

Functional imaging

organ- cell- molecular functions

tissue characterization

molecular imaging (at molecular level)

Radiology: mainly morphological imaging

Co-operation! hybrid instruments!

education (multimodality)

diagnostic algorithms

FUNCTIONS

Organs: heart (perfusion, contraction)

lung (perfusion, ventilation)

flow (blood, lymphatic)

kidney (glomerular, tubular, urinary flow)

liver (parenchymal, excretion, biliary flow)

gastrointestinal (motility, excr., absorption)

Tissue: characterization

e.g. antigens, receptors, enzyme expressions

Molecular: biochemical, metabolic processes,

e.g. angiogenesis, apoptosis, hypoxia, etc.

Genetic: DNS, mRNS (difficult), proteins easier

IMPORTANCE OF MOLECULAR IMAGING

Disease starts with molecular changes. Abnormal molecular functions before the morphologic changes.

The future is the molecular imaging, because:

1. Early diagnosis
2. Targeted diagnosis
3. Targeted therapy

MOLECULAR IMAGING METHODS

Nuclear medicine is the most important!

1. Very small amount of substance, because sensitive detection of radiation
2. Many (almost all) biomolecules can be labeled with radioisotopes (mainly PET)

MR (sequences)

Optical (light absorption)

CT

UH

MOLECULAR NUCLEAR MEDICINE
selection of the target!

Enzyms – substrates
FDG, FLT, FET, FEC, FDOPA,…
Receptors – ligands
D2, SMS,…
Antigens – antibodies (fragments)
PSMA, CEA, NCA 90, CD20,
Transzport proteins – substrates
NIS, NET,…
Deposits – binding molecules
beta-amyloid, tau protein,…

FDG IS „THE MOLECULE OF THE XX. CENTURY”

FDG is the most important molecular imaging radiopharmaceutical

F-18 is the most frequently used PET-nuclide

FDG is the most frequently used PET radiopharmaceutical

Clinical use:	Oncology	85 %
	Neuropsychiatry	5 %
	Cardiology	5 %
	Others	5 %

WHY F-18-FLUORO-DEOXY-GLUCOSE?

- „Sugar scan”
- Tumors need sugar – energy (Warburg)
  - Only uptake of glucose (hexokinase)
  - F-18-FDG-phosphate intracellular
  - Success of PET is because of FDG !
    - cost-effectiveness in oncology!
    - reimbursement!
    - (however not tumor-specific!)

FDG: GENERAL INDICATIONS in oncology

- Tumor – non-tumor
- Staging
- Restaging
- Therapeutic effectiveness?
- Therapy follow-up
- Recidiv or recurrent tumor ?
- Planning radiotherapy

FDG INDICATIONS (MEDICARE) in oncology - 2012

- Solitary pulmonary nodule
- Lung cancer
- Malignant lymphoma
- Melanoma malignum
- Oesophageal cancer
- Colorectal cancer
- Thyroid cancer
- Head and neck cancer
- Cervical (uterus) cancer
- Breast cancer

PROBLEMS OF FDG in oncology

- Not all types of tumors
  e.g. prostate, kidney, mucinous
- Physiological uptake
  brain, urinary tract, intestinal, brown fat
- Not specific (glucose uptake only)
  Inflammation, sarcoidosis

OTHER F-18 RADIOPHARMACEUTICALS in oncology

F-18-NaF	bone
F-18-cholin	prostate
F-18-DOPA	neurology, NET
F-18-FET	brain
F-18-FLT	therapy control
F-18-MISO	hypoxia
F-18-RGD	angiogenesis
etc.	

PERSPECTIVES OF NM pathophysiology: molecular changes

Apotosis	Annexin V, ML
Angiogenesis	VEGF, integrin antibodies
Hypoxia	misonidazol, FMISO
MDR	sestamibi
….	
Oncogens	F-18 oligonukleotides
Gen imaging	Gen therapy (reporter gen) HSV-Tk co-expression with F-18-deoxytimidine

etc. !!!!!

THANK YOU