IAEA Post Graduate Educational Course Radiation Protection and Safe Use of Radiation Sources

" Production of Radioisotopes and Radiopharmaceuticals"

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Radiopharmaceuticals

- Production of radionuclides
- Basic principles of localization
- Mo^{99}/Tc^{99m} generators
- Preparation of Radiopharmaceuticals
- Calculation of estimated dose
- Good Manufacturing Practice (GMP)

"Production of Radionuclides"

"Origin of Radionuclides"

Natural Radionuclides

- Dating with ^{14}C

Artificial Radionuclides

- Applications in Science (Chemistry, Physics, Industry, Agriculture, Medicine e.t.c.)

"Natural Radionuclides"

1911: Intramuscular Administration of ^{226}Ra
1913: Radioactive tracers in Chemistry
1923: Radioactive tracers RaD και ThB (^{210}Pb, ^{212}Pb) in Biology
1926: Blood flow measurements with RaC (^{214}Bi)
First radionuclidic study in Humans
1928: Absorption Studies of ^{214}Bi for Syfilis therapy
1935: First biological studies with artificially produced ^{32}P
1937: Therapy of Leukemia with ^{32}P
1938: Development of cyclotron and production of ^{131}I
1946: Introduction of reactor produced radionuclides
1946: First successful therapeutic application of ^{131}I

"Radionuclides Used in Nuclear Medicine"

Radionuclides	$T_{1/2}$	Main Radiation (MeV)	Radionuclidic Impurities
^{32}P	14.3 d	β_{max}=1.71	
^{51}Cr	27.7 d	γ=0.320	
^{57}Co	271 d	γ=0.122	^{60}Co
^{58}Cr	70 8 d	γ=0.511 - 0.811	^{60}Co
^{59}Fe	44 6 d	γ=1.10 - 1.29	^{55}Fe)
^{67}Ga	3.26 d	γ=0.093 - 0.185 - 0.30	^{66}Ga
^{75}Se	118.5 d	γ=0.136 - 0.265	
^{99m}Tc	6.02 h	γ=0.140	^{99}Mo, ^{131}I, ^{103}Ru, ^{89}Sr, ^{90}Sr
^{123}I	60.1 d	γ=0.027	^{126}I
^{131}I	8.04 d	γ=0.365	
^{133}Xe	5.29 d	γ=0.081 - 0.03 - 0.035	^{133m}Xe
^{198}Au	2.70 d	γ=0.412	^{199}Au
^{111}In	2.8 d	γ=0.173 - 0.247	
^{123}I	13 h	γ=0.027 - 0.160	
^{113m}In	104 m	γ=0.390	
^{186}Re	17.9 h	β_{max}=2.120 γ=0.155-0.633	
^{201}Tl	73 h	γ=0.068 - 0.083	
^{188}Re	88.9 h	β_{max}=1.070 γ=0.137	
^{90}Y	64.0 h	β_{max}=2.270	
^{153}Sm	46 8 h	γ=0.070 - 0.103	
^{90}Sr	27.7 y	β_{max}=0.546	

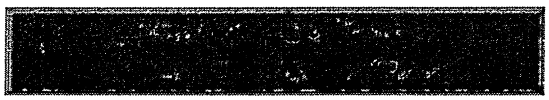
Nuclear medicine application according to type of radionuclide

Radionuclide	*Diagnostics*	*Therapy*
• Pure γ emitter e.g. ; Tc99m, In111, Ga67, I123	×	(–)
• Positron emitters (β^+) e.g. : F-18	×	–
• γ, β^- emitters e.g. : I131, Sm153	×	×
• Pure β^- emitters e.g. : Sr89, Y90, Er169	–	×
• α emitters e.g. : At211, Bi213	–	×

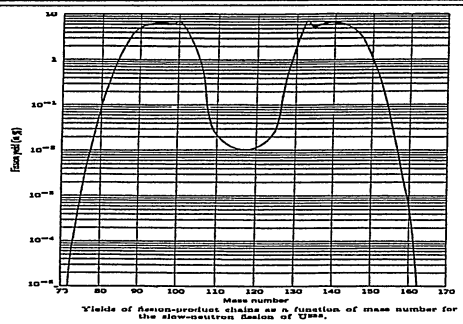
"Production of Radionuclides"

- ***Nuclear Reactor Products***
  - *Separation from Fission Products*
  - *Neutron Irradiation in the Reactor*
    - ***Generators***
- ***Cyclotron Products***
  - *Cyclotron Irradiation*

"Radionuclides from Fission"



"Radionuclides from Fission"



"Radionuclides from Fission"

- *Carrier Free Products*
- *High Radioactivity*
- *Long Live Radionuclides*
- *Low Cost Products*

"Radionuclides from Fission"

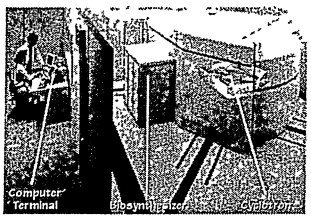
Disadvantages

Radionuclidic Impurities
Expensive Facilities
Waste Disposal Problems

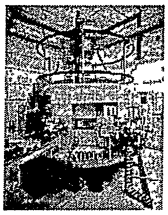
"Production of other Radionuclides"

The production of other radionuclides used in Nuclear Medicine (especially PET) involve the use of a cyclotron.

Medical Cyclotron



Industrial Cyclotron



"Cyclotron Produced Radionuclides in Nuclear Medicine"

- ***Positron Emission Radionuclides***
  - ***Anihillation Radiation***
- ***Short Lived Radionuclides***
- ***Carrier Free Radionuclides***

"Radionuclides from Cyclotron"

Disadvantages

- *Detection of Anihillation Radiation*
- *Difficult Irradiations*
- *Competitive Irradiations to the other applications of Cyclotron*

"Separation of Radionuclides"

Physical methods of separation

- Distillation
- Diffusion
- Thermal Diffusion
- Centrifugation
- Electromagnetic Techniques

"Separation of Radionuclides"

Chemical methods of separation

- Exchange Reactions
- Electrochemical Separations
- Photochemical Separations
- Chromatographic Separations

Radiotoxicity

Class A. Very high
e.g. Am-241, Cf-252

Class B. High
e.g. Na-22, Ca-45, Mn-54, Co-60, Sr-89, I-125, I-131

Class C. Medium
e.g. C-14, F-18, P-32, Cr-51, Co-57, Ga-67, Se-75, Mo-99, In-111, I-123, Au-198, Tl-201

Class D. Low
e.g. H-3, C-11, N-13, O-15, Tc-99m, Xe-133

"Radiopharmaceuticals Most Commonly Used in Nuclear Medicine"

- The primary radionuclide used for diagnosis in Nuclear Medicine procedures is technetium-99m (^{99m}Tc).
- The primary radionuclide used for therapeutic applications in Nuclear Medicine procedures is Iodine-131 (^{131}I).

"Technetium-99m"

- ^{99m}Tc has extremely favorable physical and radiation characteristics.
- 6-hour physical half-life and the absence of beta radiation permits the administration of GBq amounts without a significant radiation dose to the patient.

"Technetium-99m"

- 140-keV photons are readily collimated to give images of superior spatial resolution.
- Is readily available in a sterile, pyrogen-free and carrier free state, from ^{99}Mo-^{99m}Tc generators.

"Radionuclide Generators"

- The importance of radionuclide generators lies in the fact that they are easily transportable and serve as sources of short-lived radionuclides in institutions located in remote areas whereby contracting the services of a radiopharmacy is impracticable.

"Radionuclide Generators"

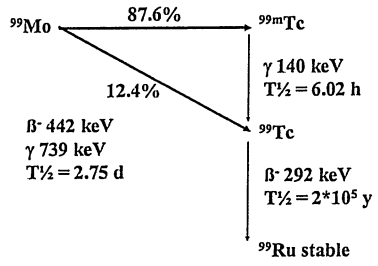
- Constructed on the principle of the decay-growth relationship between a long-lived parent and its short-lived daughter radionuclide.
- Basically, a long-lived parent nuclide is allowed to decay to its short-lived daughter nuclide and the latter is then chemically separated.

"Radionuclide Generators"

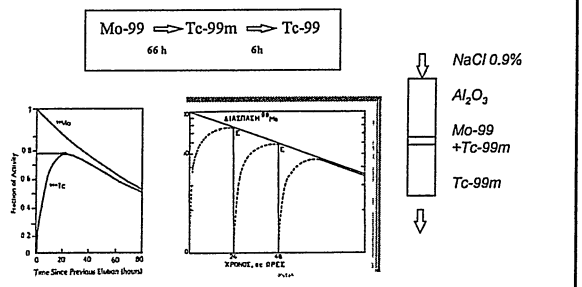
$$^{99}Zr \xrightarrow{t_{1/2}=30\text{sec},\beta^-} {}^{99}Nb \xrightarrow{t_{1/2}=3\text{min},\beta^-} {}^{99}Mo$$

$$^{99}Mo \xrightarrow{\beta^-,t_{1/2}=67h} {}^{99m}Tc$$

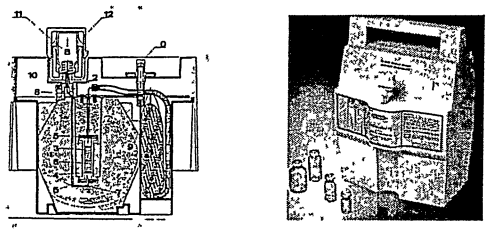
^{99}Mo-Decay



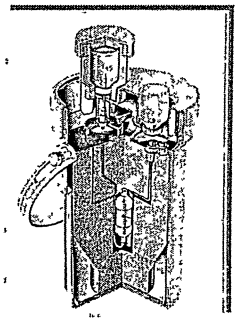
Technetium generator



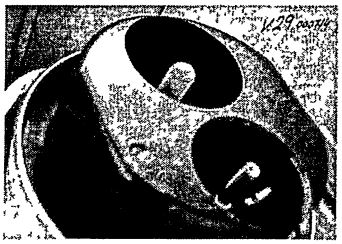
Technetium generator



Technetium generator



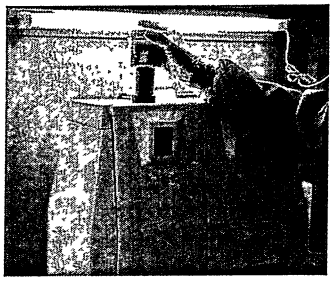
Technetium generator



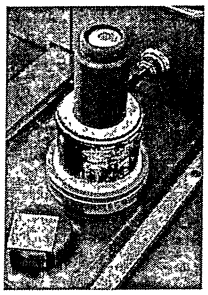
Technetium generator



Technetium generator



Technetium generator



"Preparation of Radiopharmaceuticals"

"Basic Principles of Localization"

- A radiopharmaceutical has two components: a radionuclide and a pharmaceutical.
- In designing a radiopharmaceutical, a pharmaceutical is *first* chosen on the basis of its preferential localization in a given organ or its participation in the physiologic function of the organ.

"Basic Principles of Localization"

- Then a suitable radionuclide is tagged onto the chosen pharmaceutical such that after administration of the radiopharmaceutical, radiation emitted from it are detected by a radiation detector.
- Thus, the morphologic structure or the physiologic function of the organ can be assessed.

Radiopharmaceuticals

Radiopharmaceuticals used in nuclear medicine can be classified as follows:

- ready-to-use radiopharmaceuticals
  e.g. ^{131}I- MIBG, ^{131}I-iodide, ^{201}Tl-chloride, ^{111}In- DTPA
- instant kits for preparation of products
  e.g. ^{99m}Tc-MDP, ^{99m}Tc-MAA, ^{99m}Tc-HIDA, ^{111}In-Octreotide
- kits requiring heating
  e.g. ^{99m}Tc-MAG3, ^{99m}Tc-MIBI
- products requiring significant manipulation
  e.g. labelling of blood cells, synthesis and labelling of radiopharmaceuticals produced in house

Radiopharmaceuticals

Radiopharmaceutical labeling must be performed in accordance with :

- Radiation safety regulations
- GMP requirements

Requirements of these respective regulations are sometimes conflicting :

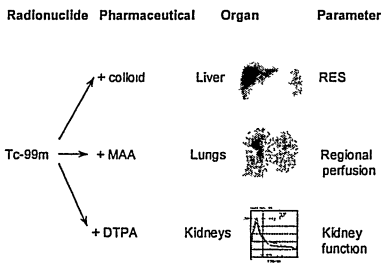
- Manipulation of radioactive material must be performed in closed area under negative air pressure
- Manufacturing of sterile injectable preparation must be performed under filtered positive air pressure (laminar flow)

"Technetium-99m"

- ^{99m}Tc-labeled radiopharmaceuticals are easily produced by simply adding $^{99m}TcO_4^-$ to many choices of "cold kits."



Radiopharmaceuticals



"Technetium-99m"

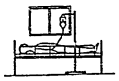
- In short, $^{99m}TcO_4^-$ is added to a vial containing a chemical compound that will bind to the radionuclide and the result is a radiopharmaceutical which, after administration, will localize in the desired patient organ to later be studied/imaged with a gamma camera.



Safe administration

Procedure for intravenous administration:

- Dispense the radionuclide into a shielded syringe
- Put the radionuclide in an infusion bottle
- Line the bottle to the patient using an intravenous catheter
- Keep the patient in bed until the bottle is empty
- Remove the bottle and the catheter and dispose of them as radioactive waste



Iodine-131

- ^{131}I is produced in a reactor.
- Used in Nuclear Medicine for both diagnostic procedures involving the thyroid and also for the treatment of thyroid disorders.

Iodine-131

- Can be administered in capsule or liquid solution form.



- Special precautions must be implemented when administering this radionuclide.

Radiopharmaceuticals in use

Examination	Radionuclide	Chemical form	Guidance level (MBq)	Effective dose (mSv)
Bone scan	Tc-99m	phosphonate	600	4.8
Brain scan	Tc-99m	pertechnetate	500	2.7
CBF	Tc-99m	HMPAO	500	5.5
Thyroid imaging	Tc-99m	pertechnetate	200	2.6
Thyroid imaging	I-123	iodide	20	3.4
Parathyroid	Tl-201	chloride	80	18
Lung perfusion	Tc-99m	MAA	100	1.2
Lung ventilation	Tc-99m	aerosol	80	0.6
Lung ventilation	Kr-81m	gas	6000	0.2
Lung ventilation	Xe-133	gas	400	0.4
Liver & spleen	Tc-99m	colloid	80	0.6
Myocardium	Tl-201	chloride	100	23
Myocardium	Tc-99m	isonitriles	600	4.2
Kidneys	Tc-99m	DMSA	160	2.5
Kidneys	Tc-99m	DTPA	350	2.2
Kidneys	I-123	hippuran	20	0.3
Tumours	Ga-67	citrate	300	36
Tumour	I-123	MIBG	400	7.2
Tumour	I-131	MIBG	20	4

Good Manufacturing Practice (GMP)

RADIOPHARMACEUTICALS

Preparation | Dispensing

Injection

Good Manufacturing Practice (GMP)

- Since radiopharmaceuticals are intended for human administration, it is imperative that they undergo strict quality control measures.
- These quality control procedures involve several specific tests and measurements that ensure the purity, potency, product identity, biologic safety, and efficacy of radiopharmaceuticals.

Good Manufacturing Practice (GMP)

- Radiopharmaceutical quality control tests fall into two categories:
  - physiochemical tests -
    - indicate the level of radionuclidic and radiochemical impurities and determine the pH, ionic strength, osmolaity, and physical state of the sample, particularly if it is a colloid.
  - biologic tests -
    - establish the sterility, nonpyrogenicity, and toxicity of the material.

Good Manufacturing Practice (GMP)

- Quality control tests for the "kits" used to prepare radiopharmaceuticals within a Nuclear Medicine department are performed at the manufacturer's facility.
- Limited quality control of the ready-to-use product can be made in the place of application, depending on special needs.

Dose Calculation

- Prescribed dose: the quantity of radiopharmaceutical activity as documented in a written directive, or in the diagnostic clinical procedures manual, in accordance with the direction of the authorized user.

Dose Calculation

- The amount (volume) of the radiopharmaceutical to draw into the syringe must be determined.
- The activity of each dosage prior to medical use must be measured.

Dose Calculation

- Because of the short half-life of ^{99m}Tc, the specific concentration of the radiopharmaceutical at the time of administration must be calculated.
- For example a 10-milliliter solution containing 1.85 GBq will have a concentration of .185 GBq/ml.

Dose Calculation

- Knowing the specific concentration, and using the decay constant of ^{99m}Tc, we are able to calculate the exact volume to draw for the desired activity to be administered to the patient.

Preparation of Radiopharmaceuticals

Name:	DPD
Composition	13 mg 3,3-diphosphono-1,2-propanedicarboxylic acid, tetrasodium salt (DPD) 0.23 mg tin(II)oxide
Usage:	Bone scintigraphy
Storage:	Kit in fridge.
Preparation:	Use a transparent vial shield. Put the kit vial in the shield. Dispense 5 ml pertechnetate (3000 MBq) in a shielded syringe. Add the solution to the vial containing the freeze dried kit. Remove an equal volume of gas to equalize the pressure. Shake the vial gently for 10s. Store the preparation for 5 min. Temporarily remove the vial from the shield and measure the activity. Use a forceps when moving the vial. Put a label on the shield. The label shall contain: Name of radiopharmaceutical, activity and activity concentration as well as date and time. Check the label against the vial. Same radiopharmaceutical? Record the preparation and sign. The preparation can be used for 5 patient examinations within 6 h from time of preparation
Storage:	Radiopharmaceutical in the shielded container and protected from light

Dispensing of radiopharmaceuticals

1. Check the label on the vial shield. Is it the required radiopharmaceutical?
2. Calculate the volume to dispense from the decay corrected activity concentration and the requested activity for the intended examination.
3. Dispense the calculated volume using a shielded syringe.
4. Temporarily remove the syringe shield and measure the activity.
5. Write a label and put it on the syringe shield. The label shall contain patient name and id number, radiopharmaceutical, activity, date and time. The label shall be signed.

Activity measurement

The activity of the radiopharmaceutical shall always be measured after preparation and before and after injection.

1. Select the isotope
2. Check the background reading and make a background adjustment
3. Put the syringe or the vial in the holder using a forceps
4. Put the holder into the chamber
5. Read the activity
6. Remove the holder and put the syringe or vial back into the shield