Radiopharmaceuticals

- Consist of Two Parts:
  - A ‘Carrier’ or ‘Vector’
  - A Radionuclide
- Directs the radioactivity to the correct part of the body
- Emits a signal which can be detected by an imaging or counting device
- Designed for each imaging application eg bone, lung, heart, liver etc etc.
- Made on-site every day as required
- Specialised skills and facilities needed

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Radio-isotope</th>
<th>Chemical form</th>
<th>Thousands of administrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone scan</td>
<td>99mTc</td>
<td>Phosphate</td>
<td>197 (29)</td>
</tr>
<tr>
<td>Lung Perfusion</td>
<td>99mTc</td>
<td>MAA</td>
<td>95 (14)</td>
</tr>
<tr>
<td>Myocardium</td>
<td>99mTc</td>
<td>Tetrofosmin</td>
<td>63 (9)</td>
</tr>
<tr>
<td>Lung Perfusion</td>
<td>81mKr</td>
<td>Gas</td>
<td>41 (6)</td>
</tr>
<tr>
<td>Kidney</td>
<td>99mTc</td>
<td>MAG3</td>
<td>30 (4)</td>
</tr>
<tr>
<td>Kidney</td>
<td>99mTc</td>
<td>DMSA</td>
<td>29 (4)</td>
</tr>
<tr>
<td>GFR</td>
<td>51Cr</td>
<td>EDTA</td>
<td>23 (3)</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>Myocardium</td>
<td>99mTc</td>
<td>Sestamibi</td>
<td>23 (3)</td>
</tr>
<tr>
<td>Lung Perfusion</td>
<td>99mTc</td>
<td>DTPA</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Myocardium</td>
<td>201Tl</td>
<td>Thallous chloride</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Lung Perfusion</td>
<td>99mTc</td>
<td>Technegas</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>99mTc</td>
<td>Pertechne-tate</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Thyrotoxicosis therapy</td>
<td>131I</td>
<td>Iodide</td>
<td>10 (2)</td>
</tr>
</tbody>
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</thead>
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<tr>
<td>Cardiac blood pool</td>
<td>99mTc</td>
<td>Normal erythrocytes</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Tumours (PET)</td>
<td>18F</td>
<td>FDG</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Infection/ inflammation/ tumours</td>
<td>99mTc</td>
<td>Exametazime</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Helicobacter Pylori test</td>
<td>14C</td>
<td>Urea</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Kidney</td>
<td>99mTc</td>
<td>DTPA</td>
<td>6 (0.9)</td>
</tr>
</tbody>
</table>

Source: Radiation Protection Division of the Health Protection Agency Report HPA-RPD-003: A Survey of Nuclear Medicine in the UK in 2003/04
Author(s): D Hart and B F Wall
Publication date: June 2005
http://www.phls.co.uk/radiation/publications/hpa_rpd_reports/2005/hpa_rpd_003.htm
Positron emitting radionuclides

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorine-18</td>
<td>110 minutes</td>
</tr>
<tr>
<td>Carbon-11</td>
<td>20 minutes</td>
</tr>
<tr>
<td>Nitrogen-13</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Oxygen -15</td>
<td>2 minutes</td>
</tr>
</tbody>
</table>

Cyclotron required

Properties of radionuclides for diagnostic use

1. Gamma ray emission only
   - high abundance
   - reduce radiation dose to patient
2. For imaging studies, gamma energy 100 - 250 kev
   - high detection efficiency
   - no significant body attenuation
   - easy to shield
3. Physical half life approx. 1.5 times duration of test
4. Simple cheap production
   - lack of radionuclidic impurities
   - high specific activity
5. Versatile chemistry

Technetium-99m

\[ ^{99m}\text{Mo} \xrightarrow{\beta, \gamma} ^{99\text{Tc}} \xrightarrow{\gamma} ^{99\text{Tc}} \xrightarrow{\beta} ^{99\text{Ru}} \]

Principal gamma energies
- \(^{99m}\text{Mo} 740\text{kev}\)
- \(^{99\text{Tc}} 140\text{ kev}\)

14% of \(^{99m}\text{Mo} \) atoms decay directly to \(^{99\text{Tc}}\)

Te generator eluates always contain \(^{99\text{Tc}}\)

Iodine-111

Half life 68 hours  \(\gamma\) rays 171 and 245kev

Cyclotron produced - relatively expensive
Highly reactive - can be incorporated into a range of radiopharmaceuticals
Useful for imaging studies
Toxic element, but available at very high specific activity
> 1.85GBq per microgram
Administered activity - up to 200MBq

Iodine radionuclides

Iodine 123  Half life 13.2h,  \(\gamma\) rays 159 kev
Cyclotron produced  - relatively expensive
Radionuclidic purity depends on production reaction
Useful for imaging studies

Iodine 125 half life 60.1 days  \(\gamma\) rays 35 kev
Te X rays (27-32 kev)
Reactor produced
Useful for non-imaging studies

Iodine 131 half life 8 days  \(\gamma\) rays 364 kev
\(\beta\) particles 606 kev
Reactor produced
Not ideal for imaging studies
Group VII elements

Technetium
Rhenium

TECHNETIUM
General Properties

• NO NATURAL STABLE ISOTOPE
  • first man-made element (1937)

• 31 Tc ISOTOPES RANGING FROM MASS 90 - 112
  • 95Tc - 97Tc decay by EC and / or β+ emission
  • 98Tc - 112Tc decay by β- emission usually to stable ruthenium isotopes

• 95Tc(60d), 99Tc(6.02h), 99Tc(212,000y) commercially available

TECHNETIUM
General Chemistry

• OXIDATION STATE (= charge on technetium atom)
  • oxidation states between -1 and +7 are known
  • +4, +7 most stable - pertechnetate ion, TcO4-
  • +1, +3, +5 forms dominate technetium chemistry
  • +2, +6 less stable / unstable

• CO-ORDINATION NUMBER (= number of donor atoms)
  • between 4 and 9
  • dependent on oxidation state
  • ≤ 5: co-ordination number 5 - 7, with oxygen occupying at least one
  • > 1, > 3: co-ordination number = 6

TECHNETIUM
General Chemistry

• DOMINATED BY FORMATION OF METAL-LIGAND COMPLEXES
  • positively charged metal ion binds to negatively charged or electron rich donor atoms on ligand molecule
  • with few exceptions (e.g. pertechnetate, Technegas) all technetium radiopharmaceuticals are complexes

• Tc FAVOURS SOFT DONOR ATOMS
  • (N, S, P, uncharged O)

REDUCTION OF TECHNETIUM

• many reducing systems used
  • sodium borohydride, sodium dithionite, sodium bisulphite, stannous chloride
  • stannous salts are the preferred reductants
  • water soluble, stable, low toxicity, effective at room temperature
  • 2 TcO4- + 16H+ + 3Sn2+ ⇌ 2 Tc3+ + 3SnO2+ + 8H2O
  • enough Sn2+ added to ensure "complete" reduction (~ 10^6 x [Tc])
  • Resultant oxidation state dependent upon several factors
    • identity of reductant and ligand, pH, temperature
**LABELLING WITH TECHNETIUM**

- $\text{TcO}_4^-$ must be reduced from $+7$ to lower oxidation state for labelling to occur.
- Reduced $^{99}\text{Tc}$ species highly reactive.
  - Reduced $^{99}\text{Tc}^+$ + chelating agent $\rightarrow ^{99}\text{Tc}^+$-chelate.
- Common donor groups include $-\text{COO}^-$, $-\text{OH}$, $-\text{NH}_2$, $-\text{SH}$.
- $\text{Sn}^{2+}$ ions may be incorporated into the complex.
- $^{99}\text{Tc}$ easily reoxidised to $\text{TcO}_4^-$.

**HYDROLYSIS OF TECHNETIUM**

- Reduced $^{99}\text{Tc}$ species hydrolyse in aqueous solution.
- Species depend on pH, duration of hydrolysis etc.
  - Includes $\text{TcO}_4^-$, $\text{TcO}_2^-$, $\text{TcOOH}^-$ - "REDUCED, HYDROLYSED TECHNETIUM".
- Extensive hydrolysis of stannous chloride at pH 6 - 7.
  - Forms insoluble colloids which bind reduced technetium.
- Any preparation will include:
  - Free $\text{TcO}_4^-$ not reduced by $\text{Sn}^{2+}$.
  - Hydrolysed $\text{Tc}$ (including reduced $\text{Tc}$ bound to $\text{Sn}$ colloid).
  - Bound $\text{Tc}$ chelate.
- Necessity for radiochemical purity measurement.

**STRUCTURE OF TECHNETIUM COMPLEXES**

- Square Planar
- Octahedral
- Square Pyramidal
- Oxotechnetium core

**$^{99}\text{Tc}^m$ HMPAO**

- $\text{ToO}_4$(L-L-HMPAO)
- Square pyramidal
- Zero overall charge
- +5 oxidation state
- 1 x tetradentate ligand

**$^{99}\text{Tc}^m$ Sestamibi**

- 6 x monodentate ligands
- $\text{Methoxy$\text{p}$-butyl$\text{i}$-}
  - Isonitrile ligands

**$^{99}\text{Tc}^m$ MDP**

- Co-ordination chemistry not simple - species formed depend on concentration, pH, reductant.
- Mixture of oligomers formed - all exhibit similar biological behaviour.
- $\text{Tc}$ as $\text{TcIV}$?
  - Octahedral complex.
**Technetium vs. Rhenium**

- Physical characteristics very similar e.g. size, lipophilicity etc.
- Rhenium complexes harder to reduce and more kinetically inert than technetium complexes
  - e.g. HEDP complexes
    - Tc: room temperature, > 99% labelling after 1 minute
    - Re: 100°C, 90% labelling after 10 minutes
  - In vivo oxidation of rhenium to ReO$_4^-$ is common

**RHENIUM RADIONUCLIDES**

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Half-life</th>
<th>Max. $\beta$ energy / keV</th>
<th>Probability per decay (%)</th>
<th>Range in tissue / mm</th>
<th>$\gamma$ energy / keV</th>
<th>Probability per decay (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{186}$Re</td>
<td>90 hours</td>
<td>1.07</td>
<td>71</td>
<td>5</td>
<td>137</td>
<td>9</td>
</tr>
<tr>
<td>$^{188}$Re</td>
<td>17 hours</td>
<td>2.1</td>
<td>100</td>
<td>11</td>
<td>155</td>
<td>15</td>
</tr>
</tbody>
</table>

**RHENIUM FOR PALLIATION OF BONE PAIN**

- $^{99}$Tc$^{m}$ MDP
- $^{186}$Re HEDP

**PALLIATION OF BONE PAIN FROM METASTATIC Ca PROSTATE**

- $^{186}$Re HEDP
- Before treatment
- 10 weeks post treatment

**Group III elements**

- Indium
- Gallium
- Yttrium
FUNDAMENTALS OF CO-ORDINATION CHEMISTRY

- interaction of a metal ion with a ligand
- resulting complex is called a chelate
- the ligand possesses donor atoms - these donate electrons to interact with the metal
- donor atoms can be hard or soft
- hard - discrete negative charges e.g. O^-
- soft - lone pairs of electrons e.g. N and S

METAL ION BEHAVIOUR

physicochemical parameters

- oxidation state (net charge)
- electronic structure
- size (ionic vs. hydrated radius)
- co-ordination number
- preference for hard vs. soft donor atoms
- thermodynamic vs. kinetic stability

METAL-LIGAND EQUILIBRIA

$$\text{LH} \rightleftharpoons \text{L}^- + \text{H}^+ (K_a)$$
$$\text{LH} + \text{M}^{3+} \rightleftharpoons [\text{L}^-\text{M}^2]^+ + \text{H}^+ (K_1)$$
$$\text{LH} + [\text{L}_3\text{M}]^+ \rightleftharpoons [\text{L}_2\text{M}]^+ + \text{H}^+ (K_2)$$
$$\text{LH} + [\text{L}_2\text{M}]^+ \rightleftharpoons [\text{L}_3\text{M}]^0 + \text{H}^+ (K_3)$$
$$3\text{LH} + \text{M}^{3+} \rightleftharpoons [\text{L}_3\text{M}]^0 + 3\text{H}^+ (\beta_3)$$
ATOMIC PROPERTIES OF SELECTED TRIVALENT CATIONS

INDIUM RADIONUCLIDES

PHYSICAL CHARACTERISTICS

- **Indium-111**
  - Cyclotron produced
  - \(^{111}\text{Cd}(p, n)^{111}\text{In}\) OR \(^{109}\text{Ag}(\alpha, 2n)^{111}\text{In}\)
  - \(T_{1/2}: 67.5\) hours; decay by electron capture; 2 gamma photons
    - energy (keV)\n    - abundance\n    - 173\n      - 89\%
    - 247\n      - 94\%

BIDENTATE LIGANDS USED FOR CELL LABELLING WITH INDIUM

- 8-Hydroxyquinoline (Oxine)
- 2-Hydroxy-2,4,6-cycloheptatrienone (Tropolone)

AMINO-CARBOXYLATE LIGANDS

- NTA (Nitrilotriacetic acid)
- EDTA (Ethylenediaminetetraacetic acid)
- DTPA (Diethylenetriaminepentaacetic acid)

GALLIUM RADIONUCLIDES

PHYSICAL CHARACTERISTICS

- **Gallium-67**
  - Cyclotron produced
  - \(^{68}\text{Zn}(p, 2n)^{67}\text{Ga}\)
  - \(T_{1/2}: 78.3\) hours; decay by electron capture; 4 gamma photons
    - energy (keV)\n    - abundance\n    - 92\n      - 42\%
    - 184\n      - 24\%
    - 296\n      - 22\%
    - 388\n      - 7\%

GALLIUM RADIONUCLIDES

PHYSICAL CHARACTERISTICS

- **Gallium-68**
  - Generator produced (\(^{68}\text{Ge}/^{68}\text{Ga}\))
  - \(T_{1/2}: 68\) minutes; decay by \(\beta^+\) emission (97%)\n  - Chelate vs. Ionic generators
    - Chelate:
      - alumina column; 0.003M EDTA eluant
      - < 0.1\% \(^{68}\text{Ge}\) breakthrough
    - Ionic:
      - Tin dioxide column; 1N HCl eluant
      - neutralisation needed for radiopharmaceutical production