Radiopharmaceutical Therapy
Part 1: Safety Aspects for Dispensing Alpha and Beta emitting Radioisotopes

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Target Audience: Pharmacists
ACPE#: 0202-0000-18-079-L05-P
Activity Type: Knowledge-based
Disclosures

George Kourlas declares no conflicts of interest, real or apparent, and no financial interest in any company, product, or service mentioned in this program, including grants, employments, gifts, stock holdings and honoraria.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Explain the electromagnetic interactions between charged particles and matter
2. Explain the potential dangers to human health while compounding alpha and beta emitting radiopharmaceuticals
3. Outline the principles of ALARA as the basis of radiation protection
4. Identify policies and procedures that would minimize exposure during the compounding process
1. Assessment Question

1. Which of the following nuclides needs to be handled in a fume hood with a corresponding chimney equipped vapor trapping filters?

A. I-131
B. Lu-177
C. In-111
D. Zr-89
2. Assessment Question

1. Which of the following is not keeping with ALARA
   A. Using syringe shields
   B. Pipetting nuclides by mouth
   C. Wearing a dosimetry badge while in a restricted area
   D. Using tongs to handle hot vials and syringes

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Activity Type:
3. Assessment Question

1. Which of the following about alpha emitter is false?
   A. Have a charge of 2+
   B. Travels a short distance
   C. Used therapeutically
   D. Lead is needed for shielding
4. Assessment Question

1. Indirect effects of radiation are mediated via free radicals secondarily produced in the interaction of radiation with:
A. Cytoplasm
B. Water
C. Plasma
D. Extracellular ions
Title

- Subhead and bullets

- Insert your slides here

- Copy and Paste selecting DESTINATION FORMATTING when copying them into the presentation deck.
Radioactive Decay: $p^+ + e^- = n$
Sources of Radiation

- **Natural Sources**
  - Terrestrial Radiation
    - U235
    - Rn86
    - Th232
  - Cosmic Radiation
    - Highest at poles and least at equator
  - Internal Radiation

- **Artificial Sources**
  - Tc99m (generator produced)
  - I-131 (reactor produced)
  - F18 (cyclotron produced)
Shielding required
Interactions of Radiation with Matter

- Radiation is either particulate or electromagnetic
- Particulate radiation includes charged particles such as alpha particles (He$^{2+}$) and beta particles (either e$^+$ or e$^-$)
- The absorption of ionizing radiation in matter involves interactions with orbital electrons and the nuclei of atoms
- During this interactive process, the radiation’s energy is partially or completely released in the absorber in several ways:
  - Excitation
  - Ionization
  - Low energy electromagnetic radiation (delta rays)
  - Bremsstrahlung
Interactions of Radiation with Matter

- **Excitation:**
  - An atom in the absorbing material absorbs energy from the passing radiation, causing an orbital electron to be excited to a high energy suborbital. The energy is then released as either UV or visible light when the electron returns to original state.

- **Ionization:**
  - An orbital electron absorbs energy from the passing radiation and is ejected from the atom.
Modes of Particle Decay

- **Alpha Decay:**
  - Alpha particles ($\text{He}^{2+}$) are high energy helium atoms carrying 2 positive charges
  - An alpha particle has the highest energy and velocity at the beginning of its path
  - On its path, multiple excitations and ionizations occur
  - The rate of excitations and ionizations increases as it slows down
  - It will eventually come to rest as a neutral helium atom
Modes of Particle Decay

- **Beta Decay:**
  - Beta particles can either positively charged (positron) or negatively charged (negatron)
  - Negatrons produce excitation and ionization by repulsive interaction of orbital electrons
  - Beta particles have a tortuous path with matter because they are easily deflected by interacting with orbital electrons
  - Beta particles can also interact with the nucleus of an atom: *Bremsstrahlung*
  - At the end of its path, a negatron will come to rest by combining with an atom that needs an electron
  - The path of a beta particle is much wider comparatively to an alpha particle
Biological Effects of Ionizing Radiation

- Most sensitive target is DNA
- Ionizing radiation within human cells cause excitation and ionization that release high speed electrons that cause further damage to biologic molecules
- The energy deposited may break the bonds of molecules that are responsible for reproduction or cellular function
- If the radiation dose is small and damage slight, the cell may be able to repair the damage
- Higher doses and dose rates can overcome the cell's ability to repair, and permanent damage will become evident within days or weeks of exposure. This is known as **deterministic effects**
Biological Effects of Ionizing Radiation

- If any repair process from radiation-induced damage is incomplete or defective, the cell may become cancerous or develop a mutation that is inheritable.

- These are known as stochastic effects which appear long after radiation exposure.

- Stochastic effects do not have a threshold dose, meaning they either occur or don’t occur.

- **Example:** A particular cancer can occur after being exposed to radiation, whether it was high or low dose exposure. However, the likelihood of developing cancer is greater after a high dose.
Biological Effects of Ionizing Radiation

- Stochastic effects can either be **somatic** or **genetic**
- The development of cancer is an example of a **somatic** event
- **Genetic** stochastic effects occur when a germinal cells sustain radiation-induced damage resulting in a mutation that is passed on to future generations
Biological Effects of Ionizing Radiation

- Simply put:
  - Deterministic effects
    - Increase with dose
  - Stochastic effects
    - Probability of effect increases with dose
Direct and Indirect Interactions of Radiation

- As previously stated the critical radiosensitive target is DNA
- Interactions within DNA or any other tissue is caused by **direct** or **indirect effects**
- Both particulate radiation and gamma ray photons release free electrons from matter
- The electrons then interact directly or indirectly with DNA
  - **Direct effects** occur when an electron interacts directly with DNA, causing a bond to break. This can occur if the ionization occurs near an chromosome
    - More probable with alpha emitters, neutrons and protons
  - **Indirect effects** of radiation are mediated via free radicals secondarily produced in the interaction of radiation with water. The free radical is highly reactive and may interact with DNA causing bond breakage
    - More probable with beta particles, gamma and x-rays
Effects of Radiation on Genetic Material

- DNA is a coiled double helix of the sugar deoxyribose, a phosphate and the bases adenine, thymine, guanine and cytosine
- The bases bond in specific pairs: guanidine with cytosine and adenine with thymine
- Flattened out DNA resembles a ladder or rails
- The sugar phosphate groups are covalently bonded and form the backbone
- There are 3 different types of radiation induced breaks in the DNA molecule
  - Single-strand break
  - Double-strand break
  - Double-strand opposite break
Effects of Radiation on Genetic Material

- **Single-strand break**
  - If a break occurs in a single rail, repair enzymes can easily repair the break. However if a free radical binds to the broken strand of DNA, blocking the enzyme's access repair is not possible.

- **Double-strand break**
  - If both rails of DNA break in such a way that base pairings hold them together repair is also possible, along with the caveat noted above.

- **Double-strand opposite break**
  - If the rails break directly opposite from each other it is more difficult to repair and can lead to disrepair and chromosomal aberrations that may cause lethal effects in the cell.
Biological Effects of Ionizing Radiation

- According to the International Commission on Radiological Protection:
  - The risk to the general population and radiation workers from typical radiation exposure in the environment or on the job is small
THEREFORE.....

DON’T PANIC
Introduction to Radiation Safety

- Nuclear Medicine professionals use ionizing radiation in the diagnosis and treatment of illness

- Ionizing radiation includes alpha, beta, and gamma
  - Therapeutic (Targeted Therapy)
    - Alpha and beta
  - Diagnostic
    - Gamma

- The basic premise of radiation safety is to maximize the benefits of NM procedures while minimizing the risk of radiation injury ALARA
As Low As Reasonably Achievable (ALARA)

- The goal of any radiation protection program is to limit radiation exposure to levels that are considered safe
- The four principles of ALARA
  - Time
  - Distance
  - Shielding
  - Planning
Taming the Beast: Targeted Radiotherapy
Alpha Emitters used Therapeutically at MSKCC

- **Ac-225**
- A Phase I/II Study of Low Dose Cytarabine and Lintuzumab-AC-225 in Older Patients with Untreated Acute Myeloid Leukemia
  - (PI's: Drs. Jae Park/Maslak Peter)
Acute Myeloid Leukemia

- Median age of diagnosis: 68
- AML does not respond well to chemotherapy/drug resistant
- Poor tolerance due to adverse effects
- Poor prognosis
Ac-225

- 225Ac having a half-life of 10 days. Decays to stable 209Bi
- 225Ac yields four alpha particles 221Fr, 217At, 213Bi, and 209Pb
  - Four α emissions produced
- The toxicities of 225Ac are related to possible sites of accumulation of its daughter products
Lintuzumab-AC-225

- Radioimmunotherapy with alpha particle-emitting constructs of the anti-CD33 monoclonal antibody HuM195 has demonstrated significant antileukemic effects
- Targets leukemic blast cells: less side effects
- May be useful in elderly AML patients unfit for intensive chemotherapy
- 2 Phases
  - Phase 1: Low Dose Cytarabine and Lintuzumab-AC-225
  - Phase 2: Lintuzumab-AC-225 alone
Beta Emitters used Therapeutically at MSKCC

- **Lu177 based**
  - Theranostics of Radiolabeled Somatostatin Antagonists 68Ga-DOTA-JR11 and 177Lu-DOTA-JR11 in Patients with Neuroendocrine Tumors
    - (PI’s O’Donaghue/Pandit-Taskar/Reidy-Lagunes)

- **I-131 based**
  - Intrathecal Radioimmunotherapy using $^{131}$I-8H9 for Central Nervous System/Leptomeningeal Neoplasms
    - (PI’s: Drs. Kim Kramer/Nai-Kong Cheung)
  - Intrathecal $^{131}$I-3F8 in Patients with GD2-Expressing Central Nervous System and Leptomeningeal Neoplasms
    - (PI’s: Drs. Kim Kramer/Nai-Kong Cheung)
Lu-117

- Beta: 490 keV
- Gamma & X-ray: 113 keV (3%), 210 keV (11%)
- Lower Large Intestine (ingestion); Lung (inhaled)
177Lu-DOTA-JR11

- Evaluate the somatostatin receptors antagonists, 68Ga-DOTA-JR11 and 177Lu-DOTA-JR11 in patients with NETs
- Biodistribution and tumor uptake of 68Ga-DOTA-JR11
- Compare the sensitivity of 68Ga-DOTA-JR11 PET with 111In-DTPA-Octreotide SPECT (the current clinical standard)
- Determine tumor and normal organ doses after administration of 177Lu-DOTA-JR11
- Obtain data on tumor response to 177Lu-DOTA-JR11.
Metastatic Leptomeningeal Neoplasms

- Neuroblastoma (NB) is the most common extracranial solid tumor in children
- Leptomeningeal space is a sanctuary site for NB mets
- Almost always fatal
- No treatment alternative exists

**8H9**

- **8H9** is a murine IgG(1) MoAb, Kd of 10 nM, 115,000 binding sites/tumor cell
- Recognizes B7H3, new member of the B7 family, restricted normal tissue expression but wide expression in many solid tumors
- Labeled by iodogen, retains immunoreactivity, 20 mCi $^{131}$I/mg 8H9

**3F8**

- **3F8** is a murine IgG(3) MoAb which binds to GD2
- Intravenous 3F8: detection and treatment of neuroblastoma
- Labeled with $^{124}$I and $^{131}$I
I-131 Sodium Iodide

- Major beta: 606 keV
- Major gamma: 364 keV
- Half-life 8 days
- Highest uptake to the thyroid
General Radiopharmacy Rules

- All personnel must wear whole body and rings while in the lab
- No food or drink in the restricted area
- Work with one radiopharmaceutical at a time
- Use syringe shields
- Survey workstation before and after compounding/SOP for spills
- Personnel garbing
- Proper waste storage
- Aseptic technique as per USP 797 guidelines
Potential Modes Internal Contamination

- Most likely routes of entry are:
  - Ingestion
  - Inhalation
  - Percutaneous absorption
  - Accidental injection
Inhalation

- I-131 volatility/aerosolized droplets
- All compounding with I-131 must be done in a fume hood with corresponding vapor trapping filters in chimney
- Charcoal packets
- Negative pressure in vials
- Radon gas?
Preventing Percutaneous Absorption

Before Entering
- Lab Coat
- Shoe Booties
- Safety Glasses

After Entering
- Double Gloves
- Sleeve Cover
- Hair Bonnet
Decontamination
Needlestick prevention devices
Scoop Method Part 1
Scoop Method Part 2
Scoop Method Part 3
Thyroid Scan
Survey Meter
Alpha Detector
Alpha and Beta Detector
# Alpha interest

<table>
<thead>
<tr>
<th>Alpha</th>
<th>Chain (AUNT)</th>
<th>Half life</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Ra224</td>
<td>Thorium</td>
<td>3.6 d</td>
<td>Manageable half life (decay)</td>
</tr>
<tr>
<td>Pb212</td>
<td>Thorium</td>
<td>11 h</td>
<td>Some may require shielding</td>
</tr>
<tr>
<td>Ac225</td>
<td>Neptunium</td>
<td>10 d</td>
<td>Evaluate facilities (hoods, effluents, etc)</td>
</tr>
<tr>
<td>Bi213</td>
<td>Neptunium</td>
<td>46 m</td>
<td>Invest in specific ($\alpha$) radiation instrumentation</td>
</tr>
<tr>
<td>Th227</td>
<td>Actinium</td>
<td>19 d</td>
<td>No thank you!</td>
</tr>
<tr>
<td>Ra223</td>
<td>Actinium</td>
<td>11 d</td>
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<tr>
<td>Ra226</td>
<td>Uranium</td>
<td>1600 y</td>
<td>No thank you!</td>
</tr>
</tbody>
</table>
Special Thanks

- Bae Philavan Chu - MSK Radiation Safety
- Matt Williamson - MSK Radiation Safety
- Serge Lyachshenko - RMIP Core
- Paul Rathod - MITS
- Earnest Rushing - MITS
- James Scoma - MITS
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Thank You!

Yeah... If you could practice ALARA while compounding, that'd be great.