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A REVIEW: RADIOPHARMACUTCAL PRODUCTION AND APPLICATION

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ABSTRACT:

In this review we understand the unique difficulties that arise during the design, (radio)synthesis, in vitro and in vivo evaluation, and clinical translation of novel radiopharmaceuticals, this review outlines general concepts related to radiopharmaceuticals for diagnostic or therapeutic applications. Given the type and location of the molecular target, the intended use, and the time constraints imposed by the relatively short half-life of radionuclides, the design of a radiopharmaceutical necessitates making decisions up front regarding the combination of an appropriate vector molecule and an appropriate radionuclide. Nonclinical validation of radiotracers is made possible by carefully planned in vitro and in vivo investigations.

Keywords: radiopharmaceuticals, radioisotopes, radionuclide, radiotherapy.

Introduction:

Radioactive materials used in diagnosis and treatment are known as radiopharmaceuticals [1]. The safe and efficient use of radioactive agents is the focus of the nuclear pharmacy specialty, which was established by the Board of Pharmaceutical Specialties in 1978.

More than 100 radioactive substances are utilized therapeutically for conditions such tumor localization, hyperthyroidism, toxic diffuse goiter, bone pain associated with skeletal metastases, and cerebral perfusion. Additionally, these radioactive medications are utilized to diagnose renal failure and infections.

Numerous radiopharmaceuticals exist, each with a unique targeting mechanism, shape, and administration method. They can be administered as simple salts or coupled to more complicated compounds.

The therapeutic radiations can be targeted non-invasively and with minimal adverse effects thanks to radiopharmaceuticals. Additionally, radioactive medications serve as non-invasive imaging tools for diagnostics, providing details on the composition and functionality of afflicted organs or tissues.

Radiopharmaceuticals :

The radiopharmaceuticals are radioactive materials that instantly break down by releasing radiation.

The half-life, which is the amount of time required for active chemicals to disintegrate to half their initial concentration, varies amongst radioactive substances. An example of the most significant radiopharmaceuticals and their half-lives is shown in table (1).

- Radiopharmaceuticals can be divided into four categories:
- Radiopharmaceutical preparation
- Radionuclide generator
- Radiopharmaceutical precursor
- Kit for radiopharmaceutical preparation

Table 1: Different types of radionuclide and their halve life'

Radionuclide	Half-life
99mTC (Technetium-99m)	6.02 hour
131I (Iodine-131)	8 d
18F (Fluorine-18)	110 min
123I (Iodine-123)	13.27 hr

67Ga (Gallium-67)	3.26 d
133Xe (Xenon-133)	5.24 d
201Tl (Thallium-201)	3.04 d
89Sr (Strontium-89)	50.53 d
125I (Iodine-125)	59.41 d
57 Co (Cobalt-57)	271.79 d
153Sm (Samarium-153)	1.93 d

Radioactivity

the different types of radioactive decays, which include alpha, beta, and gamma

1. **The alpha particle**

   Since alpha particles have a helium nucleus that is made up of two protons and two neutrons, when a radionuclide decays and releases alpha particles, its atomic number and mass will both fall by two and four, respectively. Because the alpha particles are sluggish and heavy with a large mass, they have a poor penetrating power and can be stopped by a piece of paper.
2. **The beta particle**

   The beta particles have a relatively modest mass compared to protons or neutrons since they are similar to the electron in terms of mass and charge. Beta particles can have either a positive (positron) or negative (negatron) charge. The beta particles' low mass gives them a stronger penetrating capability than the alpha particles, allowing them to pass through paper but being stopped by an aluminum sheet.
3. **Gamma rays**

   The radioactive nuclide emits gamma radiations as photons rather than particles, which indicates that they lack mass and charge. There is no change in the atomic number or mass as a result of the radionuclides' decay, which produces gamma radiations. Since gamma rays are radiation and lack mass, they have a higher penetrating power than beta particles. Gamma radiation can be utilized for diagnostics since it has no harmful effects because it is charge-free.

Production of Radionuclides :

Radionuclides used in radiopharmaceuticals are produced artificially by the radioactive decay of other radioactive atoms. This production can be carried out by any of the following methods.

1. **Radionuclides Generator**

   An ion exchange column with resin or alumina that has absorbed a long-lived parent nuclide is known as a radioisotope generator. The parent nuclide is adsorbed on the bottom of an adsorbent material, which is often a glass or plastic column used as a radionuclide generator. The daughter nuclide growth is eluted in carrier freestate with the proper solvent following the secular equilibrium, which occurs after four to five half lifetimes. 68Ga, 82Rb, 99mTc, and 113mI radionu clides are produced, with 99mTc being the most significant of them. About 85% of all imaging operations are carried out after infusions of 99mTc because of its optimal imaging energy, physical half-life, and capacity to bind to a wide variety of molecules.
2. **Cyclotron Produced Radionuclides**

   Only charged particles like electrons, protons, and deuterons may be employed with cyclotrons and other related particle accelerators. This is because the way these machines work depends on how magnetic and/or electrostatic fields interact with the particles that are accelerating. Using an electric current for acceleration and a magnetic field for control, ions are accelerated around a growing circle to create a beam of charged particles. To separate the product from the target, a variety of separation procedures are available. For separation to occur, the target and product's chemical forms must vary. Producing positron-emitting isotopes like 11C, 13N, 15O, and 18F is part of it. Cyclotron yields rely on the quantity of target atoms, particle energy, and product decay once it is formed, length of irradiation and isotope enrichment of target.When it collides with a 24Mg nucleus, a 22Na nucleus plus an alpha particle is produced. The target is exposed to the deuterons for a period of time and is subsequently processed chemically in order to separate out the 22Na nuclei.5
3. **Pile Produced Isotope**

   Today, nuclear piles, also known as nuclear reactors, produce the majority of the radioactive elements used in industry, academia, and medicine. Neutrons are produced in vast quantities by the fission process of uranium. The process is maintained by using one neutron for every uranium atom that is fissioning. The leftover neutrons are either utilized to create plutonium or to create radioactive compounds through a process called neutron activation, in which the neutrons interact with certain materials that have been added to the pile. 133Xe, 99Mo, and 131I are produced using this process.6.
4. **Thermal Neutron Reactor-produced Radioisotope**

   For thermal neutron reactor-produced radioisotopes, reactor is source of thermal neutrons. An (n, gamma) reaction occurs. It causes increase of atomic weight by one and no change in atomic number. Same element is therefore present.7 E.g. 98Mo after reaction produces 99Mo.
5. **Commonly used Radiation Sources**

   There are many radiation sources used in healthcare system. The differences relate to the position of the radiation source; external beam radiation therapy is outside the body, brachytherapy uses sealed radioactive sources placed precisely in the area under treatment and systemic radioisotopes are given by infusion or oral ingestion.8
6. **External Beam Radiotherapy**

   The radiation is beamed into the tumor from outside the body for approximately two to three minutes for each treatment. External beam radiotherapy (EBRT) or teletherapy is the most common form of radiotherapy. The patient sits or lies on a couch and an external source of ionizing radiation is pointed at a particular part of the body. In contrast to internal radiotherapy (brachytherapy), in which the radiation source is inside the body, external beam radiotherapy directs the radiation at the tumour from outside the body.9

7. **Image-guided, Intensity-modulated Radiation Therapy Intensity-modulated Radiation Therap**
   (IMRT) is used to treat patients with prostate cancer, cancers of the head and neck and cancer at the base of the skull or parts of the brain. IMRT allows the tumor to be targeted with higher doses of radiation, particularly in the vicinity of critical structures, with greater potential for a cure and greater likelihood of limiting late complications from treatment. The incorporation of imageguided technology with IMRT allows doctors to track tumor position and location while the patient is actually on the treatment table. Imageguided IMRT affords more precise coverage, allowing doctors to respond immediately to any tumor movement and, if necessary, to recalculate the radiation fields during the treatment session.10
8. **Stereostatic Radiosurgery**
   A precise, single dose of radiation is delivered in cases where tumors of the brain are adjacent to critical areas, such as the brainstem, eyes or optic nerves. Stereotactic radiosurgery further minimizes the side effects associated with conventional radiation. A neurosurgeon is present during treatment to attach a halo-like frame to the scalp to assist with proper positioning. CyberKnife is a robotic system for stereotactic radiosurgery.11 Stereostatic Radiotherapy Similar to stereostactic radiosurgery, lower doses of focused radiation are delivered with pinpoint accuracy during a series of treatment sessions that usually last between eight to 10 days. This method of multiple treatments is called “fractionation.” During treatment, a halo-like frame held in place by a mouthpiece helps position the head for treatment.12

Recentadvancement in redeopharmaceuticael:

The use of radioactive elements in diagnostic and medicinal applications, known as radiopharmaceuticals, has advanced significantly in recent years. Modern nuclear chemistry, molecular biology, and imaging technologies have been used to improve the precision and effectiveness of radiopharmaceuticals. Here,we examine some of the most important developments in the discipline, with an emphasis on improvements in cure, diagnosis, and therapy. Theranostics: The Integration of Therapeutics and DiagnosticsTheranostics' ongoing expansion is the largest shift in radiopharmaceuticals in recent years. a phrase that refers to both the integration of electronic medicine and its uses in diagnosis and therapy. Theranostics enables physicians to detect and treat illnesses, including cancer, using the same molecularly targeted medications. radiopharmaceutical for prostate cancer that targets the prostate-specific membrane antigen (PSMA).A significant advancement in treatment was made in 2022 when the FDA approved 177Lu-PSMA-617 for the treatment of metastatic castration-resistant prostate cancer (mCRPC). The radioactive isotope lutetium-177 is combined with a chemical that targets the

1. Prostate cancer cells overexpress the PSMA receptor.
   This could enhance patient outcomes by enabling precise drug delivery for imaging (PET scans) and radiation therapy regimens to treat prostate cancer. -68- PSMA for Imaging: Using methods like CT or MRI, the Ga-68)-labeled PSMA tracer is drawing interest as a potent, high-resolution PET imaging tool that can identify prostate cance. Neuroendocrine tumors (NETs) treated with targeted radiation treatment.
   Radiopharmaceuticals are also becoming more significant in the treatment of neuroendocrine cancers, which often express somatostatin receptors. Similar to yttrium-90 (Y-90) or lutetium-177 (Lu-177), isotopically radiolabeled somatostatin is used in peptide receptor radionuclide therapy (PRRT). ON. standard of care for individuals with neuroendocrine tumors that have progressed and are positive for the somatostatin receptor. An important turning point in the treatment of NETs was reached in 2018 when the FDA approved Lutathera (177Lu-DOTATATE), a medication that has a lower risk of side effects than narcotic drug use.
2. Radiolabeled Antibodies and ImmunoPET: Radiolabeled monoclonal antibodies (mAbs), specifically immunoPET and radioimmunotherapy, are being utilized more and more in the treatment of cancer. By targeting particular tumor markers, these monoclonal antibodies allow for tailored radiation therapy to be administered to the tumor. One promising new treatment for non-Hodgkin lymphoma (NHL) patients is 177Lu-labeled rituximab. Rituximab is an antibody that targets B cells' CD20 antigen. It can directly administer targeted radiation therapy to brain malignancies when paired with the radioactive isotope Lutetium-177. According to clinical research, this method of treating NHL has positive outcomes with little targeted harm . Early tumor detection and treatment response monitoring are made possible by recent advancements in PET (PET imaging employing radiolabeled antibodies). Nowadays, radiolabeled antibodies are being utilized to improve treatment, give molecular insights into cancer, and boost the sensitivity of PET scans. Novel radiopharmaceuticals for Alzheimer's disease therapyIn addition to cancer, neurological illnesses, especially Alzheimer's disease (AD), are included in the field of radiopharmaceuticals. Positron tomography (PET) molecular imaging is crucial for AD diagnosis and follow-up. The primary offender is the use of 18F-florbetapir, a PET radiopharmaceutical that binds to the brain's amyloid plaques, which are a defining feature of Alzheimer's disease and are marketed under the name Amyvid. It is now an FDA-approved AD diagnostic tool. making it possible to diagnose patients early and with greater accuracy (Avid Radiopharmaceuticals, 2012). In therapeutic trials, targeting radiopharmaceuticals to nodes—another characteristic of AD—has showed promise for brain imaging, yielding crucial data regarding the course of the illness.

Safety Considerations and Regulatory Perspectives:

Radiopharmaceuticals are useful in modern medicine, especially in oncology, cardiology, and neurology, because they combine the medicinal or diagnostic effects of radiation with target molecules. However, there are unique safety concerns about the use, handling, disposal, and management of these materials because of their radioactivity. To safeguard patients, healthcare professionals, and the environment, these concerns are meticulously handled through safety and regulatory protocols.

Radiation Safety:

Talk about precautions and legal requirements.1. Safety measures for radiopharmaceuticals: measures to lower radiation exposure, increase the drug's efficacy, shield staff from disease, and manage the destruction of electronic devices. Safety of Patients Dosimetry of Radiation: Reducing radiation exposure to patients while optimizing therapeutic benefit is a major safety concern when using radiopharmaceuticals. Radiopharmaceuticals are often employed in low doses that are unlikely to cause significant harm for diagnostic purposes. On the other hand, chemotherapy, including radioligand therapy (e.g., 177Lu-PSMA-617 for prostate cancer), requires additional radiation and dosimetric precise calculations. The target dose in clinical practice is the lowest dose for tissues like the kidney and bone marrow and the greatest dose for the tumor. In order to attain this equilibrium, Calculating dosimetry is crucial. Personal Protective Equipment (PPE) for Healthcare Workers' Protection: PPE, including as gloves, crystals, and radiation protection signs, should be used by healthcare personnel who handle radioactive chemicals. When handling and processing radiopharmaceuticals, use shields to prevent personnel from being exposed to needless radiation. They are precise and keep an eye on the right levels via electrical signals. Avoid it. Robots or remote equipment are frequently used to handle radiopharmaceuticals in order to protect containers and minimize direct exposure. displayed.

A. Environmental protection and waste managementManagement of Radioactive Waste:

Radiopharmaceutical waste, such as antibiotics, Strict protocols should be followed while disposing of vials and patient discharges. Depending on the isotope activity and the material's half-life, radioactive waste is categorized as either low-level waste (LLW) or high-level waste (HLW). Before being disposed of, waste is reduced to a safe level. In order to prevent electrical current from flowing while being stored, lead shielding is frequently utilized. step before to disposal. To find possible leaks and make sure there are no electrical risks in the region, do routine assessments using electrical equipment like Geiger-Muller counters. All patient care conforms with safety regulations. Equipment for radioactive safety and security. Safety Standards of the International Atomic Energy Agency series. This procedure covers every facet of producing radiopharmaceuticals, including high-quality raw materials, production procedures, labeling, packaging, durability, and quality criteria, such as purity and sterility (WHO, 2011).

B. National Authorities for Regulation:

United States Food and Drug Administration (FDA): The FDA in the US regulates radiopharmaceuticals according on whether they are considered biologics or medicines. To guarantee that radiopharmaceuticals are safe and effective for their intended application, the approval procedure entails extensive testing and early investigations. Additionally, the FDA carefully calculates radiation doses and performs post-marketing surveillance to track the safety of approved devices by gender

The Committee for Clinical Use in Human Use (CHMP) evaluates radiopharmaceuticals to make sure they are efficient, safe, and effective. To guarantee adherence to EU regulations, EMA collaborates with national regulatory bodies "Peptide receptor radionuclide therapy using 177Lu-DOTATATE in patients with advanced neuroendocrine diseases.

C. Radiopharmaceuticals GMP:

Good Manufacturing Practice (GMP)-compliant facilities are required to make radiopharmaceuticals. GMP guarantees that radiopharmaceuticals are produced under strict quality control, labeling, storage, and sterility guidelines in a controlled setting. According to the World Health Organization (2011), these procedures are crucial for preserving the radiopharmaceutical's stability, effectiveness, and safety. (2011). Principles of Good Manufacturing Practice. series of technical reports from the World Health Organization. Standards for Radiation SafetyMedical Radiation Protection: Guidelines for radiation protection in healthcare facilities are provided by the International Commission on Radiation Protection (ICRP). In order to achieve clinical goals while minimizing radiation exposure to patients and healthcare personnel, ICRP advocates ALARA (as low as feasible). the amount of radiation needed for therapy or diagnostic. protection against medical radiation. Publication 105, ICRP. To reduce the risk of radiation exposure to patients, healthcare professionals, and the environment, safety precautions are required. International and transnational organizations control the process to guarantee the safety, efficacy, and efficiency of radiopharmaceuticals. The benefits of e-medicines can be realized while lowering related risks by adhering to safety protocols and legal requirements.

Regulatory Difficulties:

Examine regulatory viewpoints in various geographical areas.In contemporary medicine, radiopharmaceuticals—which blend radioactive isotopes with medicinal or therapeutic agents—are crucial, especially in the domains of neurology, cardiology, and oncology. However, these employees are subject to numerous rules since they use technological equipment. Although enhancing safety, efficacy, and efficiency is the aim, different jurisdictions, including the US, Europe, and Asia, have rather different approaches to regulating radiopharmaceuticals. This section highlights the distinctiveness of each organization and how they handle the complications of radiopharmaceuticals by comparing the laws and difficulties in these fields.

Advantages of Radiopharmaceuticals in Healthcare System

- It can be used as diagnosis and treatment of patient.
- It can provide fast onset of pain relief.
- It is common to cure cancer.
- Can treat multiple disease sites.
- Widely available mode of treatment.
- Directly treats tumor, especially useful for bone metastasis.
- Single dose is effective for some patients.
- Nuclear medicine tests can be performed on children.
- Nuclear medicine procedures have no side effects and are completely safe.42

Disadvantages of Radiopharmaceuticals in Healthcare System

- When multiple fractions are given, it may produce prolonged inconvenience and discomfort for patients.
- Higher doses of head and neck radiation can be associated with cardiovascular complication, thyroid dysfunction and pituitary axis

dysfunction.

- Nuclear medicine tests are non-recommended for pregnant women, because unborn babies have a greater sensitivity to radiation than children or adults.
- Filling in patient's teeth, dental braces and permanent bridges may cause some distortion around the mouth area.
- Can produce some allergic reactions.
- It has a radiation risk.
- Myelosupression may occur, especially with prior chemotherapy.43

Important points:

A. **Precision and Personalized Medicine:**

The creation of radiopharmaceuticals that include particular disease indicators can enhance therapy results, lessen injury to healthy tissues, and increase the efficacy of treatments. 177Lu-PSMA-617, a biomarker-driven treatment for prostate cancer, is an example of how molecular targeting can enhance both therapeutic and diagnostic results.Theranostics: Oncology and neurology are using more and more theranostics, which are medications that can be used both for diagnosis and treatment. Personalized intervention from the point of care is made possible by the use of radiopharmaceuticals for diagnosis and treatment, which enhances patient outcomes and treatment planning. New developments in radionuclide treatment: The identification of alpha-emitting radionuclides, such actinium-227 and radium-223, opens up new therapeutic options for cancer that is challenging to cure, particularly metastatic disease. It has a favorable outlook. Cancer treatment is being revolutionized by their high cytotoxicity and capacity to deliver potent radiation directly to the tumor while causing the least amount of damage to adjacent tissue. Imaging advancements: Since the introduction of hybrid imaging methods like PET, SPECT, and PET/MRI, radiopharmaceuticals have been crucial to noninvasive diagnosis. In the cases of cancer, neurological disorders, and insect-induced cardiac disorders in particular, this technique may facilitate precise diagnosis, early detection, and improved treatment response tracking.

B. **Immunoradiotherapy**:

Immunotherapy and radiopharmaceuticals together have a lot of potential to improve the precision and effectiveness of cancer treatment. In addition to using radiation to target tumors, radiolabeled antibodies and checkpoint inhibitors also help the immune system identify and eliminate cancer cells.

C. **Innovations in Manufacturing and Regulation**:

New treatments can now be developed and approved more quickly because to the simplification of the regulatory framework for radiopharmaceuticals. Technological developments in automated synthesis and on-site production of radiopharmaceuticals will lower costs and increase accessibility, particularly in remote places.

D. **Overcoming Obstacles**:

In spite of these developments, a number of obstacles still need to be addressed, such as productivity and strict reagent control because of their radioactivity. has been widely embraced. (particularly cancer) capacity to go along its course. They are the foundation of true medicine in the twenty-first century because of their capacity to target illnesses at the molecular level in conjunction with state-of-the-art technologies.The potential of radiopharmaceuticals will increase with further research and clinical data, giving patients with conditions ranging from cancer to neurological disorders fresh hope. Prolonged advancements in immunoradiotherapy, theranostics, and new radionuclide therapies hold the potential to transform medicine in the future and push the limits of successful diagnosis and self-limiting treatment. The future of medicine is becoming more individualized, more focused, and more successful in treating even the most difficult and complex illnesses by utilizing the power of radiopharmaceuticals.

Application of radiopharmaceuticals

the treatment of bone metastasis Bone metastasis is the most common type of pain in cancer patients. It reduces patient quality of life and linked with many complications, such as hypercalcemia, bone fractures, spinal cord compression. Treatment is mainly palliative by using analgesic drugs, antiinflammatory drugs, radiotherapy and surgery. Various radionuclides are used to provide analgesic treatment of bone metastases, including samarium-153 (Sm-153), phosphorus-32 (P-32) and strontium-89 (Sr-89). Samarium-153 is a radionuclide with 1.9 d half-life which can be used for diagnosis and treatment of bone metastasis due to the emission of both beta particle and gamma radiation. Samarium153 has the ability to target the bone tumor, it goes to the source of cancer bone pain and emits the beta particles resulting in pain relief. In the majority of patients, pain relief occurs within the first week of therapy. Phosphorus-32 used to suppress hyper proliferative cells. It emits beta particles with a physical half-life is 14.3 d. It decays in the form of beta particles with a maximum energy of 1.71 MeV allow it to be useful in case of bone metastasis . Strontium-89 chloride is administered intravenously, it deacys and emits beta particles. The physical half-life of Strontium-89 is 51 d. It has the ability to accumulate metastatic bone lesions in higher concentrations than in healthy normal bone. After intrsvenous injection, the Strontium-89 acts as calcium it selectively cleared from the blood and localized in the bone minerals

Radionuclide	diagnostic use Reference
Technetium-99 m	Used in diagnosing of cardiac amyloidosis
Chromium-51	Used in diagnosis of pernicious anemia

Fluorine-18	Used in positron emission tomography to assess alternations in glucose metabolism in brain and cancer
Holmium-166	Used in the diagnosis of liver cancer
Iodine-125	Used in diagnosis and evaluation of the glomerular filtration rate of kidneys
Gallium-67	Used in tumors imaging
Potassium-42	Used in determination of exchangeable potassium in coronary blood flow
Iodine-131	Used in studying the function of the thyroid gland
Rubidium-86	Used in determination of myocardial blood flow

CONCLUSION:

A variety of radiopharmaceuticals are currently on the market and play a significant part in illness diagnosis. However, with the advent of several novel radionuclides and radiopharmaceuticals for the treatment of neuroendocrine, metastatic bone pain, and other malignancies, this area of nuclear medicine has recently experienced a notable expansion. The discipline of radionuclide treatment is now experiencing a very fascinating and exciting time and is expected to continue growing and developing over the next several years.

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