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RADIOPHARMACEUTICALS: A MINI REVIEW OF APPLICATIONS AND INNOVATIONS ON NUCLEAR MEDICINE

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ABSTRACT

Radiopharmaceuticals are a group of medicines known for their radioactive agents, known as radioisotopes. They are employed in various areas, primarily clinics for the diseases' diagnosis or treatment. Their structure comprises a radionuclide (regulates the physical characteristics) and a drug (determines the biological behavior). The following review describes the general and innovative applications of radiopharmaceuticals, the manufacturing process, and the regulation they must have to be administered safely. This work showed various functions of radiopharmaceuticals in the pharmaceutical industry for diagnostic and therapeutic purposes (^{99m}Tc, ^{131}I, ^{67}Ga, ^{153}Sm, ^{201}Tl, ^{81m}Kr, ^{223}Ra, ^{18}F, ^{90}Y, ^{186}Re, and ^{169}Er) and the innovation being developed to treat pathologies more efficiently and safely. The rigor required for the manufacturing as well as the quality control during their preparation, dispensation, and use was also appreciated. Concerning Costa Rica, their utilization continues to grow, so it is essential to maintain strict security protocols.

KEYWORDS: radiopharmaceuticals, Costa Rica, diagnosis, therapy, quality control.

INTRODUCTION

Radiopharmaceuticals are a group of medicines that contain radioactive agents called radioisotopes. They are employed in various areas, primarily clinics for the diseases' diagnosis or treatment. These molecules emit radiation by themselves, differing from contrast media, and their utilization depends on the type of radiation emitted. If the consideration is for diagnosis, those whose radioactive decay emits electromagnetic radiation such as X-rays (Roentgen radiation), γ rays, or β+ particles (positrons) are usually selected. On the other hand, if the destination is the treatment of a pathology, a radioactive decay through the emission of α particles, β- particles (electrons), or Auger electrons is contemplated.[1,2,3,4]

They are made up of a radionuclide (regulates the physical characteristics) and a drug (determines the biological behavior). Radionuclides are unstable nuclides that spontaneously decay to a more stable atom through the emission of particles, electromagnetic radiation, isomeric transition, or capturing electrons. The drug is the organic or inorganic chemical fraction that determines its biodistribution. In other words, it carries the radionuclide to the site of interest within the body.[4]

Their administration is systemically most of the time. Because of that, they must comply with the basic requirements of injectable and systemic compounds such as sterility, non-pyrogenicity, toxicity, among others. Additionally, they can locate specific tissues thanks to their biomolecular properties.[2,4]

These drugs can be divided into four categories according to the criteria established by the International Pharmacopoeia of the World Health Organization (WHO). They are:[1]

- Radiopharmaceutical preparation: this is a ready-to-use medicinal product that contains a radionuclide, which is essential for its medical application. It may be appropriate for one or more diagnostic or therapeutic applications.
- Radionuclide generator: consists of a system in which a radionuclide with a short half-life (daughter radionuclide) is separated from a radionuclide with a long half-life (parent radionuclide), and later, it is employed to produce a radiopharmaceutical preparation.
- Radiopharmaceutical precursor: it is a radionuclide for the radiolabeling process, resulting in a radiopharmaceutical preparation.
- Kit for radiopharmaceutical preparations: it consists of a vial containing the components without radiopharmaceutical preparation's radionuclides. A specific radionuclide is added, or the appropriate radionuclide is diluted before medical consideration. It is a multidose

vial in most cases, and its production may require additional steps (boiling, heating, filtration, and buffering). They are typically designed to be applied within 12 hours of preparation.

Around 5 % of radiopharmaceuticals have therapeutic uses, while 95 % are for diagnosing certain pathologies. Among their main advantages, they are minimum invasive, the radiation to which the patient is exposed is very low, they are painless, there is no restriction on the age to be administered, and they have a reasonable cost (depending on the disease). Likewise, they allow metabolic or functional evaluation of organs and tissues, unlike other available tools.[5]

Therefore, this review aims to describe the general and innovative applications of radiopharmaceuticals, the manufacturing process, and the regulation they must have to be administered safely.

GENERAL USES

The two primary goals are diagnostic and therapeutic. They are detailed below.

Diagnosis

The diagnosis involves the administration of a low dose of a drug linked to a specific radionuclide. When decaying, they emit electromagnetic radiation (gamma or Roentgen radiation), which has high penetrating power but is absorbed in a limited way by the tissues. Its detection outside the patient's body requires a gamma or positron emission tomography (PET) camera.[2,6]

Unlike X-rays, which only allow soft tissue to be visualized with a contrast agent, nuclear medicine diagnostics allow the structure of organs and tissues and their function to be observed. The level of radiation absorbed by the tissues or organs can indicate their level of functioning. Therefore, if someone wants to study organs or tissues at the anatomical level, the first option is contrast radiography, while for their respective functions, nuclear medicine is considered.[6,7]

By measuring the behavior of the administered radionuclide, several conditions can be determined, including tumors, infection, and hypertrophy. Evaluation of blood circulation is also possible. Areas where radionuclide accumulates can be observed by devices capable of

detecting hot spots. For its part, cold spots are areas where it is not absorbed, causing scans to appear dark or with little shine.[7]

There are many procedures to perform scans and get diverse images. For example, there are the planar ones, where the gamma camera remains static, and 2D images are achieved. As a complement, there are more complex tests such as single-photon emission computed tomography (SPECT). Axial "cuts" are made of the organs of interest as the gamma camera rotates around the patient. In this way, the images are like those of computed tomography (CT) scan. Likewise, the PET scan can be contemplated, obtaining results in 3D, when combining with the data from SPECT.[7,8]

All these procedures are widespread in the diagnosis of diseases. The most common tests are cardiac, lung, bone, renal, thyroid, brain, and breast scans. Each one has a specific radionuclide since, depending on the organ or tissue of interest, there will be certain radiopharmaceuticals with a greater affinity for a given region. Thus, the drug to be used and the type of scintigraphy to be performed must be correctly chosen.[6,7,8]

Treatment

Radiopharmaceuticals for therapeutic purposes fulfill the function of administering a high dose of radiation to a target tissue, destroying malignant or hyperactive cells with minimum damage to the surrounding healthy tissues. The destruction is based on the cell death of the target tissue or organ through irreversible damage to the nuclear DNA, inducting cuts in the double helix, with the consequent inhibition of cell proliferation.[9,10,11]

In this therapy, the biological effect is obtained by the energy absorbed from the radiation emitted. For a radionuclide considered for a therapeutic approach, it must emit radiations with a relatively short penetration, not affecting the cells of healthy tissues and organs.[5,10]

Furthermore, unlike in diagnostic procedures, a radionuclide whose life is long enough to reach the target tissue or organ before it begins to decay is needed. Besides, it must be short enough so that the dose absorbed in healthy tissues is low and they are not affected.[3,9]

Likewise, they must comply with a series of properties related to the type of radiation.[9,10,11] They are detailed in the next section.

Types of radiation decay

There are three types of decay for therapeutic reasons. These are the beta and alpha decays and the emission of Auger electrons.[9,10,11,12] Differing highly in mass, energy, and range, such factors must be contemplated for the intended biological effects and potential therapeutic function.[9,11]

The β- particle emitters have been utilized because they have a low linear energy transfer (LET) and act by producing free radicals capable of causing DNA damage. In addition, radionuclides with this emission type are occasionally accompanied by a decay of gamma emissions, which is advantageous. Although gamma radiation does not play a role in destroying any malignant tissue or any other disorder, it does serve as a diagnostic tool. Therefore, it can obtain scintigraphic images and determine the radiopharmaceutical location, along with the treatment's effect on the body. Plus, β- emissions have a much greater range than other particles, being able to destroy adjacent tumor cells, even if these are not the target of the administered radiopharmaceutical.[9,10,11]

On the other hand, alpha and Auger radiation have high LET. Such a situation makes it more efficient to destroy tumor cells. However, they are not very penetrating radiation, making it necessary to transport them through the cell membrane, and be in the cell nucleus or its vicinity.[9,10,11]

Radiopharmaceutical therapies are limited by the risk of their administration and biodistribution, both associated with the pathologies to be treated. Nonetheless, each time it evolves to be more specific and safer, minimizing its risk, as will be explained later.

RADIOPHARMACEUTICALS USED IN COSTA RICA

As shown in **Table 1**, most of the radioisotopes available in the Costa Rican market are for illness diagnosis. Despite this, some, when administered at high doses, can function as therapeutics, including ^{131}I. Additionally, the combination of the radioisotope with the drug determines the affinity for a specific tissue since radioisotopes alone are not administered.[3,5,9]

Table 1: Radiopharmaceuticals commonly utilized in Costa Rica.[4,5,9,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28]

Radioisotope	Emission	Diagnostic use	Therapeutic use
^{99m}Tc	γ	Location of stroke (already diagnosed), evaluation of pulmonary perfusion, blood pool, bone, brain, cardiac, hepatobiliary, nasolacrimal drainage system, planar breast, renal, salivary gland, and thyroid imaging agent, myocardial perfusion agent, and lymphatic mapping	
^{131}I	β- and γ	Hyperthyroidism diagnosis, performance of the radioactive iodine uptake test to evaluate thyroid function, localization of metastases associated with thyroid malignancies, evaluation of glomerular filtration, total blood and plasma volumes, cardiac output, cardiac and pulmonary blood volumes and circulation times, protein turnovers studies, heart and great vessels delineation, and localization of the placenta and cerebral neoplasms	Hyperthyroidism and thyroid carcinoma
^{67}Ga	γ	Lymphoma detection and osteomyelitis diagnosis	
^{153}Sm	β- and γ		Relief of pain in patients with confirmed osteoblastic metastatic bone lesions
^{201}Tl	X-ray and γ	Diagnosis and localization of myocardial infarction, diagnosis of ischemic heart disease or atherosclerotic coronary artery disease (along with exercise stress testing), and localization of sites of parathyroid hyperactivity	
^{81m}Kr	γ	Ventilation agent to detect patients with suspected pulmonary embolism	
^{223}Ra	α		Castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases
^{18}F	β+	PET imaging, specifically for bones' images	
^{90}Y	β	Radiolabeling (radioimmunotherapy procedures)	
^{186}Re	β-		Bone pain palliation and synovectomy
^{169}Er	β-		Treatment of arthritis during inflammatory flare-ups of the small joints of the hand and foot, when intra-articular corticosteroid therapy fails

RADIOPHARMACEUTICAL PRODUCTION

Most radioactive material for clinical procedures does not occur naturally but is produced by two main physical processes: nuclear fission and particulate bombardment (neutrons or charged particles). Both alter the neutron-proton relationship in the nucleus, causing an unstable isotope or radionuclide.[29,30]

The bombardment of charged particles (alpha particles, protons, or deuterons) employs a cyclotron or other particle accelerator. This equipment irradiates the nucleus of the selected atom with charged particles (if the bombardment consists of neutrons, the phenomenon occurs in a nuclear reactor). The following general equation can visualize this process (the element of interest and the bombarding particle are on the left and the products on the right):[29,30]

$$^{A}_{Z}X + \text{n (neutron)} \rightarrow {}^{A+1}_{Z}X + \gamma$$

This equation can be abbreviated in the following representation: $^{A}_{Z}X$ (n,γ) $^{A+1}_{Z}X$. After the bombardment is complete, the daughter isotope must be physically separated from any nuclei that have not been modified, as well as any contamination present (carrier-free isotope).[1,29,30]

For this process, it is vital to have high purity reagents so that radionuclides with sufficient activity are obtained. Isotopes with particle accelerators almost always involve the transmutation (change of Z) from one element to another. Such a process facilitates their separation, obtaining carrier-free isotopes of stable elements. Nevertheless, in the case of ^{99}Mo, it is produced from ^{98}Mo, and there is no alteration in Z. This process where no transmutation occurs is caused by neutron bombardment that does not result in an elemental change. Their separation is complicated, and radionuclides free of stable elements are not obtained.[1,30]

Radionuclides are also produced by nuclear fission. Those formed through such a process must be controlled in a careful way to minimize the radionuclidic impurities.[1,29,30]

The isotopes with an excess of neutrons experience beta emissions. In contrast, those produced through the bombardment of charged particles tend to be deficient in neutrons and decay by emission of positrons.[1,30]

It is essential to note the existence of carriers. It is an inactive form of the material, either isotopic with the radionuclide or non-isotopic, but chemically similar, which can be found during manufacture or dispensation or added to increase the activity of the radionuclide without generating a physiological effect on the patient. Thus, when speaking of carrier-free radionuclides, these correspond to preparations formulated without carriers, indicating that they have not undergone specific activity dilution processes.[1]

Additionally, radionuclide generating systems have been implemented in clinical laboratories since the equipment may not be available on site. These isotopes have shorter half-lives and decay by an isomeric transition. The most common systems include columns using a parent radionuclide with a relatively long half-life affixed to an ion exchange column. In the case of the ^{99}Mo-^{99m}Tc generator, Mo is the parent element attached to an alumina column that performs the ion exchange function and decays over time to its daughter isotope ^{99m}Tc, with a shorter half-life (from approximately 67 hours to 6 hours).[29] The product is bound to the column loosely so it can be washed or physically removed. There is a wet system with a reservoir of saline water (0.9 % NaCl) and a vacuum-sealed vial to facilitate the flow of this saline water through the column. In contrast, in a dry system (a standard procedure in radiological clinics), a specific amount of saline water in a vial is put into an inlet that permeates the column and through a vacuum chamber at the other end allows the respective flow.[29,30]

For this way of processing, it is necessary to consider that the elution times must be spaced apart to allow the accumulation of the daughter radioisotope in the column, regardless of the system used. The maximum product activity obtained occurs when the decay rate is equal to its production rate. This scenario allows determining the quantities produced of the relevant radioisotope.[29,30]

EXCIPIENTS AND ANTIMICROBIAL AGENTS IN FORMULATIONS

Radiopharmaceutical preparations can contain various types of excipients. These substances are allowed by individual monographs in the specific dosage form.[1]

As an adjunct, the preparations are facilitated in multidose containers. Therefore, they must have preservatives (antimicrobial agents) to guarantee the formulation sterility (whose preferred sterilization method is filtration). In case of not containing such components, despite being multidose, it should be utilized within 24 hours after the first dose.[1]

QUALITY CONTROL

Quality controls are essential in any production or formulation line within the pharmaceutical industry. Radiopharmaceutical preparations are no exception. Radionoclidic, radiochemical, and chemical purity, half-life measurement, pH, sterility, bacterial endotoxins, pyrogens, labeling, and storage tests are highlighted. Besides, Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP) must be followed.[1]

Moreover, there are quality controls for the equipment used in its manufacture. Some prominent tests are dose calibration and seal source. For gamma cameras, uniformity, energy spectrum, energy resolution, and collimator integrity, among others, are required. In the case of equipment such as SPECT, assays of the center of rotation, head tilt angle, system performance, and spatial resolution in air must be made. In addition, the specifications for gamma radiation equipment must be met. As for PET scanners, tests such as temperature, attenuation correction, tomographic uniformity, sensitivity, and spatial resolution are necessary.[30]

COSTA RICAN LEGISLATION FOR RADIOPHARMACEUTICAL PRODUCTS

Radiopharmaceuticals are drugs that require different legislation. For this reason, they are one of the exceptions of the Central American Technical Regulation (RTCA, for its Spanish acronym). In the context of Costa Rica, the Ministry of Health mentions the requirements regarding with employment, management, import, export, and destocking of radioactive materials and ionizing radiation-generating devices, transport of radioactive materials, and capacitation and training to people involved with radiological protection services along with services for installations with radioactive materials and ionizing radiation-generating devices.[31]

The declaration and technical sheets on these drugs have their guidelines (and unique health records). Furthermore, for its management, it is necessary to develop procedure manuals in various areas, such as industrial and clinical. As a complement, there are emergency cards to follow during their transportation that have information about: isolation distance, emergency protocol, United Nations (UN) number, institution name, product name, registration number, radionuclide (s), activity, physical and chemical form, description of the material and its container, special warnings, incompatibilities, and contamination.[31,32] The elaboration of these files requires a high degree of knowledge, for which the professional training is highly specialized.

There is an important element around exposure to radioactivity and the necessary protective material within the same legislative area. Constant exposure to radiopharmaceuticals, together with their preparation and handling, requires crucial protective equipment. Plus, a maximum exposure time during working days must be considered, which is defined on a scientific basis on the risks of continuous exposure, even if the requested protective equipment is available. Such legislation includes anyone who is exposed to radioactivity, including patients.[33]

INNOVATION AROUND RADIOPHARMACEUTICALS

Given the growing applications of radiopharmaceuticals, various efforts have been made to optimize their preparations, diversify chelating agents, study their pharmacokinetics, bioavailability, distribution, and toxicity, and explore possible diagnosis approaches and treatments, especially in the oncology area.[34,35,36,37]

In terms of innovation, they can be visualized as three significant edges: the radionuclide, the vehicle (vector), and the therapeutic target. In this way, it can be the use of new radionuclides in therapies or those already approved (such as ^{99m}Tc),[38] with a new automated production process, new vehicles that increase bioavailability, more stability with chelating agents or aptamers, or giving them a new therapeutic and/or diagnostic function.

In their preparation, new techniques have been implemented to optimize the procedures and their corresponding purification. For example, a chip capable of purifying radiopharmaceuticals for PET imaging by continuous flow pervaporation has been produced. The objective of these microfluidic chips is to offer an alternative to the micro-scale distillation process done, obtaining a product with the specifications of the European Pharmacopoeia.[39]

Another relevant aspect is the automation processes, which have become standard practices, alluding to a two-step one-pot synthesis. Examples of this are [^{11}C]glyburide (labeled anti-diabetic drug) and [^{18}F]fluoroestradiol or [^{18}F]FES (a drug that interacts with estrogen receptors). Even though the procedures for developing these radiopharmaceuticals require diverse conditions by their very nature, the implementation of this methodology avoids unwanted secondary products in the first and facilitates the preparation and purification of the second. Therefore, the importance of these methodologies is appreciated in obtaining faster processes to elaborate and purify the molecules, especially within the clinical area.[40,41]

On the other hand, regarding the intended purposes, heavy metal radionuclides in complexes with different chelating agents showed high safety and good biological activity. In addition, the applications are expanded by utilizing targeted vehicles, such as aptamers. In this way, several therapies achieved greater specificity (substantial advances appreciated in preclinical studies), although non-specific interactions remain a challenge. The employment of aptamers labeled by radionuclides provides greater distribution, better renal clearance, and faster access in tumor cells.[42,43,44]

Other considerations studied have been in immune disorders, mainly those associated with inflammation, such as anti-TNFα (from tumor necrosis factor α) antibodies and interleukins, and specialized radiopharmaceuticals in neuroinflammation and heart inflammation cases. At the diagnostic level, better images have been obtained in SPECT and PET with ^{99m}Tc and ^{68}Ga to visualize and diagnose immune problems, such as autoimmune ones, having a growing impact within these diseases.[45]

For the oncology field, in treating bone metastasis,[46] which leads to pain, fractures, neurological symptoms, and hypercalcemia in patients, phosphate-based radiopharmaceuticals have shown improvements in the patient's symptoms, reducing pain. Two examples are ^{166}Ho-DOTMP and ^{177}Lu-EDTMP.[47] These drugs have been investigated and continue to make important contributions.

Another example is [^{64}Cu][Cu(ATSM)] and Cu^{2+}. They are used to diagnose and measure oxygen levels in tumor cells, resulting in vital information for patient management. Studies have been done in people with lung, breast, brain, and colon cancer. This molecule is still under study in preclinical studies and clinical trials.[48]

Besides, the design of chelating agents is another innovative element. Methionine-conjugated ^{99m}Tc demonstrated high affinity and increased cytotoxicity in tumor cells in *in vitro* assays and *in vivo* mouse models.[49]

Finally, the peptide-based PET radiopharmaceuticals are associated with poor stability *in vivo* against proteolysis. Nevertheless, structural modifications have been made, such as cyclization, peptide bond substitution, and modifications of the C- and/or N-termini to increase their stability. The idea is to take advantage of these molecules' potential for SPECT and PET imaging.[50]

CONCLUSIONS

This work showed various applications of radiopharmaceuticals in the pharmaceutical industry for diagnostic and therapeutic purposes (^{99m}Tc, ^{131}I, ^{67}Ga, ^{153}Sm, ^{201}Tl, ^{81m}Kr, ^{223}Ra, ^{18}F, ^{90}Y, ^{186}Re, and ^{169}Er) and the innovations that are being developed to treat pathologies more efficiently and safely. The rigor required for the manufacturing and the quality control during their preparation, dispensation, and use was also appreciated.

Concerning Costa Rica, their use continues to grow, so it is essential to maintain strict security protocols. Besides, an increase in the number of functions associated with them is expected in the future, especially considering the early opening of the cyclotron at the Universidad de Costa Rica.

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