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Radiopharmaceuticals: Production, Physics, and Clinical Applications in Nuclear Medicine: A Short Review

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ABSTRACT

Introduction: The use of radioactive atoms in medicine is growing, particularly in nuclear medicine, where radiation is emitted from the body. Radiopharmaceuticals or radiotracers are artificial short-living radioisotopes labeled with special pharmaceuticals. There are around 1800 radioisotopes, but only around 200 are suitable for general applications. There are four methods for generating radioisotopes: reactor-producing, neutron activation, charged acceleration, and radioisotope generators. Cyclotrons are used to produce many other radioisotopes for medical applications. Physical and biomedical characteristics are crucial for radiopharmaceuticals for clinical use. Physical aspects include the type and energy of radiation, mother and daughter radioactive elements, purity, and half-life of radioactives. Biomedical considerations include easy adhesion to biomolecules, a dynamic time course in the body, toxicity, and high tissue targeting. Radiopharmaceuticals used in diagnosis differ from those used in therapy, with positron emission tomography (PET) using radioisotopes, and gamma-emitting radioisotope-labeled radiopharmaceuticals suitable for SPECT imaging. Over 90% of radiopharmaceuticals are used for diagnostic purposes.

Conclusion: Nuclear medicine, as an inevitable part of modern medicine, follows different methods to create more effective diagnostic and therapeutic radiopharmaceuticals with respect to several physical and biological considerations.

Keywords: Radiopharmaceuticals, Nuclear Medicine, Neutron Activation, Particle Accelerators.

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1. Introduction

With the discovery of radioactive materials, a new window to the world of medicine is opened. The combination of radioisotopes and their transferring molecules, under the general name of radiopharmaceuticals, gave rise to a branch of science called nuclear medicine. Natural radioactive material, because of its long half-life (several to several million years) and high atomic mass, could not occupy a permanent place in the field of nuclear medicine. With the development of nuclear knowledge and the production of artificial radioisotopes, this branch of science was revived (1). Different methods have been introduced for the production of artificial radioactive materials, all of which are based on disturbing the balance between the number of neutrons and protons in the nucleus of stable atoms and thus making them unstable. These procedures include uranium 236 products in the nuclear reactor, neutron activation, charged particle accelerators, and radioisotope generators (2).

Each method produces radioisotopes with different properties. Those radiating gamma rays and positrons are used for imaging, and radioisotopes radiating beta-minus rays have therapeutic applications in nuclear medicine. Currently, about 1800 different radioisotopes have been discovered, with a small number (about 200 types) of which, passing through the filter of physical and biological considerations, can be used for medical purposes (3). At present, a large number of studies are about to be conducted for the development and expansion of the procedures used for the production of radioactive materials.

Another problem is the labeling of the radioactivity component of the carrier molecules (pharmaceuticals). The carrier molecule should have the characteristics to be highly absorbed at the desired sites and could carry the radioactive component to its target. Despite the developments in the production of radiopharmaceuticals in the field of diagnosis and therapy, the need to explore isotopes with better physical and biomedical standards (suitable half-lives, easy and inexpensive production, high purity, no toxicity, an appropriate dynamic course of medicine, and its ability to bind to radioactive materials, having enough energy) is strongly felt (4).

2. Methods

This article reviews the methods of producing artificial radioisotopes and the characteristics of the isotopes derived from each method, the standards for assessment of radioisotopes for clinical applications, the carrier molecules and labeling radioisotopes with them, and the latest

therapeutic approaches of radiopharmaceuticals. In the present review article, for searching the documentation, we used Google Scholar, PubMed, and the Web of Sciences and the keywords "diagnostic radiopharmaceuticals", "therapeutic * radiopharmaceuticals", "cyclotron", "artificial radioisotope", "reactor-based radioisotope", "radiopharmaceutical label * technique *". In the information banks, the papers published over the years 2000–2018 were selected by selecting the option of review articles and the use of the main articles. In the present review article, for searching the documentation, we used Google Scholar, PubMed, and the and the Web of Sciences and the keywords "diagnostic radiopharmaceuticals", "therapeutic * radiopharmaceuticals", "cyclotron", "artificial radioisotope", "reactor-based radioisotope", "radiopharmaceutical label * technique *". In the information banks, the papers published over the years 2000–2018 were selected by selecting the option of review articles and the use of the main articles.

Of the approximately 150 documentaries reviewed, the materials were selected in accordance with the following criteria:.In the beginning, the relation of the documentation to the research title was evaluated by the search engine. These contents were divided into three categories: Internet contents, books, and articles. The criterion for selecting Internet sites after having a relation with the title was to have an academic or educational suffix (of ac or edu). After review, subjects that were more comprehensive than the rest were selected. Among the books selected for research, the criterion for their selection was their relevance to the research title and their availability. Among the available articles, those relevant to the title were evaluated in terms of their relevance to the research. After reviewing the abstract of the article or studying the conclusion, documents that were discussing only physical aspects without the medical aspects were deleted.

3. Results

3-1. Radioisotope production

Stable atoms have a balanced number of neutrons and protons in their nucleus. An equal number of protons and neutrons does not indicate the balanced state (stability) of the nucleus. Natural radioactive atoms have no application in nuclear medicine, which is due to their long half-lives and sometimes their high atomic mass; therefore, for medical applications, it is necessary to produce artificial radioactive materials. The general principle is to disturb the balance between the number of protons and neutrons in the nucleus by

bombarding protons, neutrons, or other charged particles toward the nucleus (5).

3-2. Radioisotopes produced by nuclear fission reactions

The atoms used commonly for nuclear fission are natural uranium (U-235 and U-238). The U-235 in the nuclear reactor is converted to the U-236 by absorbing low-speed neutrons ("thermal neutrons," whose speed is reduced by heavy water). This uranium is highly unstable and suffers fission reactions; it is usually broken down into two lighter atoms and some neutrons (6). The fission of the U-236 aften results in the production of one atom with an atomic mass of about 105–85 and another atom with a mass of about 150–130. Rarely, two atoms are produced with the same atomic weight. In this process, a large amount of heat energy is also produced. More than 100 atoms of 20 different elements from the fission of U-236 are produced in the reactor (7). One of the most important fission products is molybdenum (Mo-99). The probability of producing this atom is 7% in nuclear fission (7).

$$^{99}_{39}\mathrm{Y} \xrightarrow{\beta^{-}(1.5s)} {}^{99}_{40}\mathrm{Zr} \xrightarrow{\beta^{-}(21s)} {}^{99}_{41}\mathrm{Nb} \xrightarrow{\beta^{-}(15s)} {}^{99}_{42}\mathrm{Mo}$$

All the radioisotopes produced by the nuclear fission have extra neutrons than their stable state, and they radiate beta-minus rays to reach stability. Also, due to the fact that in reactors along with these products, usually their isotopes are not produced, the products are career-free, and their separation is relatively easy (8).

3-3. Radioisotopes produced by neutron activation

In this method, which is carried out in the atomic reactor, neutrons are incident with stable atoms and are absorbed into the nucleus of atoms. In this case, the balance between the number of neutrons and protons is disturbed, and two types of reactions occur: the neutron-gamma reaction (n, γ) and the neutron-proton reaction (n, p) (9). In the neutron-gamma reaction (n, γ), the nucleus of the target immediately receives a neutron, a new radioisotope element is obtained, and immediately a gamma photon is radiated from the nucleus. The target atom (mother) and the new element (daughter) in this reaction are radioisotopes of each other (10).

$$^{A}_{Z}\mathrm{X}\ (\mathrm{n,p})\ {}^{A}_{Z-1}\mathrm{Y}$$

In the second reaction (n, p), the nucleus of the target atom receives one neutron and immediately releases one proton (11).

$$^{A}_{Z}\mathrm{X}\ (\mathrm{n,p})\ {}^{A}_{Z-1}\mathrm{Y}$$

One of the general features of the products of neutron activation is the presence of extra neutrons in the nucleus of the

products more than the balance state, which means that these radioisotopes also irradiate beta-minus rays. Most of the products of this process are not carrier-free, which means that because of the presence of radioisotopes, their isolation and purification will be less (1).

3-4. The radioisotopes produced by accelerating charged particles

Accelerators electrically accelerate charged particles like protons, alpha, and deuteron. Then accelerated particles hit a stable atom, and due to its high energy (10–30 million electron volts), they overcome the nuclear repulsive force and enter the nucleus. Consequently, the balance between the protons and the nucleons of the nucleus is disturbed, and a radioactive atom is produced. There are different types of reactions of accelerated charged particles hitting atoms, such as the (p,n) reaction, in which, after the incident of accelerated protons with atoms, neutrons are immediately ejected from the nucleus and the radioisotope is generated (12). Another example is the (d, n) reaction, in which, after the accelerated deuteron incidents with the nucleus, one neutron is ejected and a new radioisotope is produced (13).

$$^{A}_{Z}X\ (d,n)\ ^{A+1}_{Z+1}Y$$

Various types of particle accelerators are present, such as Van de Graff accelerators, linear accelerators, and cyclotrons. The latter, called cyclotron, is involved in the production of radioisotopes used in nuclear medicine. One of the features of yields produced by cyclotrons is the presence of extra protons in the nucleus as compared to neutrons in their balanced states, which means that this isotope radiates beta-positive particles (positrons). These radioisotopes are used in the Positron Emission Tomography (PET) modality. Cyclotron products are also career-free. The advantage of using cyclotron is that the production of nuclear waste materials is lower than with other methods. Radioactive atoms such as F-18, C-11, and O-15 can be produced by cyclotrons (14).

3-5. Radioisotope generator

One of the most widely used radioisotope production methods in nuclear medicine is the radioisotope generator, which is used to produce radioisotopes with a short half-life and should be produced and used at that nuclear medicine center (the generator size is as large as a tea-brake). The radioactive element (the mother element) in the generator is converted into a new radioactive element (the daughter element) by irradiation. Then the daughter element is removed (elution) from the generator and

can be used. The most common radioisotope generator in nuclear medicine is molybdenum-technetium **(**Mo-Tc)**.** The molybdenum-99 element is placed in the generator reservoir and, with a half-life of 66 hours, is converted to the technetium-99 radioisotope. When the technetium concentration reaches its maximum, it is taken away from the generator and used for medical purposes (15).

3-6. Radio-labeling techniques for pharmaceuticals

There are several approaches to labeling. The first method is direct substitution. The radioactive atom is being substituted for a stable atom in the molecule. Consequently, molecules retain their biological properties and pass their biological pathway unchanged. The most common and interesting application is the replacement of the C-11 radioisotope with one of the C-12s in the glucose molecule, which produces C-11 glucose, which is used in PET scans. The C-11 has a half-life of 20 minutes, which needs a cyclotron in the same center to produce the C-11 (16).

The second approach is to produce an analog. The analog of a molecule is a synthetic that has undergone some changes. The most practical example is the ^{18}FDG analog. The F-18 radioisotope is replaced with the hydroxyl (OH) group of the second carbon in the glucose molecule and generates an analogue of glucose, ^{18}FDG. The F-18 has a half-life of 110 minutes, compared with C-11 glucose. The ^{18}FDG analog has a long half-life, and it does not need to have a cyclotron at the PET scan center (17, 18).

The ^{18}FDG analog in PET scan imaging plays a significant role in showing the metabolism of the body since glucose utilization indicates the rate of metabolism. Tumors with high metabolism use more glucose, F-18s are absorbed more by the tumor, and more positrons are emitted from the tumor (19). Another prominent point relevant to the ^{18}FDG analog is that this compound can only pass the first phase in its metabolic pathway, making it much easier to analyze the metabolic information (18). But some of the analogs have dissimilar behavior to their original composition, and understanding their metabolic pathways may be complex (20). For the labeling of larger biological compounds, such as antibodies and peptides, radioisotopes are chelated and then bonded to the compound. Chelation means fixing a radioisotope in a ring that protects the atoms from reacting with other compounds. The chelation allows the radioisotope not to react with other molecules and to remain attached to the antibody or peptide. Then the antibody or peptide can take itself to the infected site,

and the dose of radiation reaches that point. This method is most often used in therapeutic nuclear medicine. Radioisotopes in these methods are usually those radiating beta-minus rays (21).

3-8. Labeling of Nano-Assemblies with Radioisotopes

Recent developments in nanotechnology have led to the use of these small particles as radioisotope carriers in diagnosis and therapy in nuclear medicine. For example, gold nanoparticles that are attached to iodine-125 have been effective for the imaging of infections and inflammation (22). The high potential of these nanoparticles for targeted therapy of cancer has led the researchers to focus on these methods (23). Some nanoparticles tend to bind to the cell wall of cancerous cells and enter the cells without energy consumption (22).

3-9. Using "Cold Kits" labeled with radioisotopes

These kits contain non-radioactive compounds that are usually labeled with the Tc-99 radioisotope and can be used immediately after combining with it. These kits contain specific ligands for absorption into specific organs, buffers (NaOH and HCL), ascorbic acid (as a stabilizing agent for the kits), and NaCl (for the isotonicity of the final solution) (24).

3-10. General considerations for radiopharmaceuticals

In order to select an appropriate radiopharmaceutical, there are certain evaluation criteria; if they fulfill them, they can be used clinically in nuclear medicine. The type of rays irradiated and their energy are the first criteria. In diagnostic applications, gamma-ray-emitting radioisotopes with energies ranging from 100 to 600 keV, as well as positive beta-rays, are used. For therapeutic applications, beta- and minus-rays and alpha-rays are used. The physical half-life of the radioisotope is also very important. The best half-life of radioisotopes used in nuclear medicine is from a few minutes to a few days.

The degree of purity of the radioactive material should be as high as possible, and the special activity of the radiopharmaceuticals should be suitable. The radioisotope must be easily attached to the pharmaceutical without losing its physical properties. The duration of the dynamic course of radiopharmaceuticals is also significant; for example, labeled radioisotopes with antibodies usually require several hours to several days to bind to their target tissues, and during this period, the composition of radiopharmaceuticals should not change. These materials should not have toxic

effects on the body. It is still preferable to produce radiopharmaceuticals with the lowest cost (1).

Conclusion

The production of radioisotopes with specific characteristics to be utilized in nuclear medicine has always been one of the main issues of this profession, and various methods have been developed for the production of radioisotopes. Also, the need for carriers that take radioisotopes to the target sites and organs has led to the discovery and invention of new compounds. These compounds (radiopharmaceuticals) are now used for the diagnosis and therapy of many diseases. Despite recent development, the complexity and expensive nature of the production process, the low specificity of radiopharmaceuticals to bind to the target sites in the body, and low-purity products stand out as challenges to this approach.

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