RADIOPHARMACEUTICALS IN NUCLEAR MEDICINE: EVOLUTION AND ROLE IN DENTISTRY

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Abstract

NUCLEAR MEDICINE is the branch of medicine and medical imaging that uses radiation emitted by a radio-pharmaceutical to provide information about both the structure and function of organ systems within the body thereby aiding in the diagnosis and treatment of a disease. This unparalleled branch of radiology concerns with the diagnostic and therapeutic use of radionuclides. The most striking feature that distinguishes Nuclear Medicine from other Imaging Modalities is that Nuclear Medicine aids in imaging the metabolism and other physiological process of specific organs in human beings and thereby unveil the various functional and biochemical processes with accuracy which makes it a dynamic and very powerful tool in diagnosis and treatment of diseases. The role of this review article is to understand radiopharmaceuticals and its indications in dentistry and also the recent imaging techniques of the era!

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Introduction

Nuclear Medicine, essentially a molecular and cellular imaging technique is a combination of various sciences which include Medicine, Engineering, Physics, Chemistry and Mathematics. It has developed profusely and is now used in almost all fields of medicine including Neurology, Cardiology, Orthopedics, Oncology and many more. Radioisotope is a major entity of radiopharmaceuticals.

Medical radioisotopes are labelled or tied with specific biological molecules which are called as Radio-Pharmaceuticals. They are administered in traces therefore they are also called as Tracers. Nuclear medicine is an indispensably unique imaging technique that provides imaging at molecular and cellular level which makes it highly important in early diagnosis, treatment and prevention of the disease and is an imminent component of patient care. Nuclear medicine is a brand new discipline of Medicine and can be dated back to the end of the second world war in 1940`s.

The introduction of I-131 for treating thyroid disease in 1964, followed a few years later by I-131 thyroid imaging, marks the beginning of nuclear medicine;[1] it was the discovery of 99m technetium in 1937 and the subsequent development of the first commercial 99m-Tc generator in 1964 that led to the tremendous growth of nuclear medicine.[1] Today over 10,000 hospitals worldwide use radioisotopes in medicine, and about 90% of the procedures are for diagnosis.[2,3] 35 million in-vivo

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procedures are performed annually in the world, including 20 million in the USA, 9 in Europe, 3 in Japan and 3 in rest of the world.[4] In developed countries (26% of world population) the frequency of diagnostic nuclear medicine is 1.9% per year and the frequency of therapy with radioisotopes is about 1/10th of this.[5]

PRODUCTION OF RADIOISOTOPE:

Radioisotope production was eventually implemented in the gigantic gas diffusion plant at Oak Ridge, Tennessee but it was an impractical method as it proved to be expensive and could supply only naturally occurring isotopes.[6]

Radioactivity can be induced in light elements by supplying them with excess energy. This can be brought about by exposing the elements to neutrons in a nuclear reactor or to charged particles like proton, deuteron or alpha particle in a cyclotron.[7] Radioisotopes can be produced in a Nuclear Reactor by exposing appropriate target material to neutrons in the reactor, thereby causing nuclear reaction to occur which leads to production of desired radioisotope. Thus, they are called as Neutron Rich Radioisotopes.[7]

Cyclotron was derived by Lawrence and Livingston in 1932 to accelerate charged particles like protons, deuterons and alpha which are accelerated to high energy levels and are allowed to impinge on the target material. Thus they are called as Neutron depleted or Proton Rich Radioisotopes.[7,8,9]

APPLICATIONS OF RADIOISOTOPES:

Many applications employ a special technique known as the tracer technique. A small quantity of radioisotope is introduced into the substance to be studied and its path is traced by means of a Geiger Muller (G.M) counter. The high sensitivity of nuclear radiations enables it to trace various biological processes.[7,8,9]

DIAGNOSTIC RADIOPHARMACEUTICALS

90% of all in vivo nuclear medicine procedure is carried out for diagnostic purposes.[3] Diagnostic radiopharmaceuticals were developed based on the principle that every tissue and organ in human body absorbs particular chemicals. Thus Radiopharmaceuticals were developed i.e., radioisotope labelled with a particular tracer/targeting chemical which when injected into the body via intravenous route/intraperitoneal/orally/inhalation; distributes in the whole body. It then accumulates in the particular organ and is subsequently taken up by that organ, undergoes bio-distribution and emits radiation & thus aids in diagnosis. The excess is excreted through natural means. This makes Nuclear Medicine an essentially molecular and functional Imaging Technique.[3]

It allows physician to identify at a metabolic and cellular level what is going on inside a person's body. It images both hard and soft tissues. In addition to pinpointing the underlying cause of the diseases, physicians can actually see how disease is affecting other functions in the body.[3] It is mainly used for critical conditions which include Cancer, Hormonal diseases, diseases affecting Brain, Heart, Bones, Lungs, Liver, Kidneys, Spleen, Gastro-intestinal tract and other organs. Diagnostic radiopharmaceuticals can assess the blood flow to various organs of the body, the lymphatic flow of the tumours, functioning of various organs, assess the metabolism, perfusion of organs and thus aids to confirm a diagnosis.[1]

It aids as a Biomarker for various tumours and in staging of tumours; also as an indicator of prognosis. Most importantly Diagnostic radiopharmaceuticals can help differentiate between benign and malignant tumors and consequently in evaluation of metastases. Diagnostic radiopharmaceuticals also finds its applications in sites of inflammation, thrombosis and atherosclerosis.[1] A diagnostic radioisotope must emit gamma rays of sufficient energy to escape from the body and it must have a half-life short enough for it to decay away soon after imaging is completed. The mean effective dose is 4.6 mSv per diagnostic procedure.[5]

THERAPEUTIC RADIOPHARMACEUTICALS

An ideal therapeutic radioisotope is the one which is a strong beta emitter and which emits just enough gamma radiation to enable imaging eg. Lutetium-177.[5] Various examples where therapeutic radioisotope finds its use are to treat thyroid diseases (uses I-131), to reduce the bone pain caused by metastatic cancer in Polycythemia Vera (uses P-32), in Coronary Brachytherapy (to reduce coronary restenosis following angioplasty). It is also used in external irradiation also called as Teletherapy in which Co-60 is used.[5] Currently Targeted Alpha Therapy (TAT) or Alpha radioimmunotherapy is gaining importance for the treatment of Lymphomas, Brain Gliomas, Prostate Cancer, Ovarian Cancer, Colorectal Cancer, Melanoma and Leukemia. Lead-212 is used in TAT.[5] With any therapeutic procedure, the aim is to confine the radiation to well-defined target volumes of the patient. The doses per therapeutic procedure are typically 20-60 Gy.[5]

The main difference between Diagnostic and Therapeutic radioisotope is that the Diagnostic radioisotope should not be absorbed by the tissue. Therefore the energy released by the radioisotope must be deposited in the Camera Crystal where as the radioisotope used for therapeutic purpose should be absorbed in the tissues i.e. the energy released must be deposited in the diseased tissue which can cause destruction of the malfunctioning cells and thereby cease the further growth of the malfunctioning cells.[1]

APPLICATIONS IN DENTISTRY

Nuclear medicine and radioactive tracers have applications in dental research wherein the trace amounts of these radioactive materials can be precisely measured and distinguished from the mass of inert element in the tooth.[10] Radioactive decay from radiopharmaceutical helps in studying the metabolic activities associated with bones and teeth which aid in various applications in dentistry and research pertaining to dentistry which include: [10]

- Disorders related to mineralization and calcification.
- Investigating various conditions like enamel hypoplasia secondary to dental fluorosis.
- In periodontics for periodontal diseases.
- In conservative & endodontics for caries and its protection and the dental material microleakage studies.
- In nutritional and endocrine effects leading to root resorption and other disturbances.
- Age determination by nuclear tests.
- Scintigraphy for evaluating the osteoblastic activity around implants & bone scintigraphy.
- Indication of active alveolar bone loss.
- Various TMJ diseases diagnosis.

They are discussed in detail below:

1.BONE SCAN

Various bone disorders like osteomyelitis, bone tumours, inflammatory and metabolic disorders can be diagnosed via bone scan. Bone scan is highly efficient in the diagnosis as it can assess mineral loss of even minor amount i.e. 10-15% mineral loss can be visualized in a bone scan when compared to 30-35% of that of conventional radiographs. Thus bone scan can detect the true positive results making the test highly sensitive.[11] Tc-99m has the characteristic property of binding with calcium ions and hence aid in the formation of calcium phosphate. It is well known that osteoblasts play the utmost important role in ossification by incorporating calcium phosphate at the particular site. This property of Tc-99m binding with calcium ions has made it an essential radiopharmaceutical in conducting bone scan. Tc-99m accumulates in areas with increased ossification and those which are rich in vascular supply. Tc-99m can appear either uniformly distributed, photopenic (decreased intake) or hot(increased intake). When there is no abnormality the uptake of the radionuclide is uniform, therefore it is bilaterally symmetrical. Lesions with decreased uptake include early osteomyelitis, multiple myeloma, avascular necrosis, prosthetic joint, local vascular compromise and post radiation lesions.[12]

Lesions with increased uptake maybe called "hot" lesions and can be visualized in bone tumours i.e. Benign, malignant and metastatic tumours (distribution varies accordingly e.g. metastatic spread can be seen more in specific organs like breast, lungs etc.), metabolic disorders (like fibrous dysplasia, cherubism, osteopetrosis, Paget's disease) & inflammatory disorders (like condylar hyperplasia and TMJ derangement and osteoarthritis, rheumatoid arthritis). Calcifications, inflammatory and hormonal changes can lead to activity in soft tissues.[12]

For increased efficiency a triple phase bone scan is conducted; sometimes a 4-phase bone scan may be conducted for excellent results.[12] Recent advances in bone scan is SPECT which makes the image 3-dimensional thereby making the diagnosis more precise.

2.GALLIUM SCAN

Gallium has a unique property of accumulating non-specifically in areas which are infected, inflammed (as gallium has affinity to transferrin)[13] or with excessive abnormal cell growth. This is because gallium has a characteristic property of affinity for rapidly dividing cells i.e. WBC and tumour cells.[12] It increases the specificity thereby combating the disadvantage of bone scan. It can be used along with triple bone scan for the final confirmation of osteomyelitis and also as a marker for the treatment of osteomyelitis. A limitation of gallium scan is that it does not give a marked differentiation between the bone and the adjacent soft tissue inflammation.[13]

3.SALIVARY GLANDS IMAGING

Tc-99m readily accumulates in the acinar cells of the salivary glands. This property of Tc-99m finds its application in visualizing various salivary glands thereby helps in evaluating the salivary gland function and detection of pathology if any (like atresia, agenesis, hyperplasia, calculi, fistula, inflammation, neoplasm etc).[12]

Therefore it is a key adjunct to the major investigative procedure. Decreased uptake of the radionuclide is seen in cases associated with xerostomia like Sjogren's syndrome or inflammation of chronic type[14] whereas acute inflammation is associated with increased uptake.[15]

4.LYMPHOSCINTIGRAPHY

It is the scintillation scanning of lymph nodes and its associated lymphatics following an injection of a radiopharmaceutical. Tc-99m sulfur colloid is injected subcutaneously. Sentinel lymph node is the first node to be affected in malignancy and thus sentinel lymph nodes helps in the identification of tumour because of the property of accumulation of radioisotope in the malignant neoplastic cells such as melanoma, breast cancer, thyroid cancer, gastric and small-non cell lung cancer. This sentinel lymph node mapping prevents the elective neck dissection in oral cancer cases and axillary clearance surgery in breast cancer cases. It the primary first echelon node draining the site of a primary malignancy.[12]

5.PET SCAN AND SPECT

PET (positron emission tomography) scan is a contemporary imaging modality which gives anatomic, biochemical and physiological detail of the lesion. SPECT is a nuclear imaging modality which emphasizes on the metabolic functioning of the tissues or organs and gives 3-dimensional images. PET and SPECT provides the highest sensitivity and ability to study physiological biochemical processes without affecting them which makes it similar to optical imaging.[16]

PET is a powerful tool in differentiating the benign from malignant tumours therefore is widely used in the field of oncology. The principle behind PET scan is the labelling of 18F-Fluorodeoxyglucose (FDG) with a radioisotope.[12] The positron emitted due to the radioactive decay is assessed by PET scanner and thus image is formed. It produces 3-dimensional images of the organ and the associated lesion. It serves as a good indicator of treatment and prognosis of carcinoma apart from staging of tumour & detecting the primary occult tumour.[12] It can even detect tumour at N0 stage.[12] It is also used to diagnose various cardiac disorders and neurological disorders like parkinsonism and dementia.[16]

PET scan emphasizes mostly on the true negative result therefore shows increased specificity when compared to sensitivity. The hybrid PET-CT scanner uses the combined technology of PET and CT scanner and thereby evaluates diseases through simultaneous functional and morphostructural analysis to give a more precise result.[16] It gives 30% better diagnosis than with traditional Gamma cameras alone. It is a very powerful and significant tool which provides unique information on a wide variety of diseases from dementia to CVS diseases to oncology.[5]

SPECT(single photon emission computed tomography) is similar to PET except it has an additional feature of showing the blood flow to tissues and organs and also various metabolites and metabolic reactions occurring in the body. It uses gamma rays and a gamma camera to acquire 3-dimensional images.[17] It is used in tumour imaging (localising the tumour), thyroid and neuroimaging and also in bone scanning. SPECT/CT has enhanced the staging and diagnosis of tumours of neuroendocrine origin by using somatostatin receptor scinitgraphy.[17]

BENEFITS v/s RISKS

The amount of radiation in a typical nuclear imaging procedure is comparable with that received during a diagnostic X-ray, and the amount received in a typical treatment procedure is kept within safe limits.[12]

The amount of radiopharmaceutical given to a patient is just sufficient to obtain the required information before its decay.[3] Thus it is very safe; no distress is caused to the patient and since the excess is excreted via natural means there is no sign of the test ever done.

RECENT ADVANCEMENTS

Nuclear Medicine has been in use since 1930's and the world has experienced major evolutions in this field. The gradual advancement from Rectilinear scanners to Gamma cameras and then from single and multiheaded cameras which allowed the dynamic count versus time studies and finally the 3-dimensional imaging which lead to the establishment of more precise, sophisticated and non-invasive techniques like PET, PET/CT, SPECT, SPECT/CT, mmR Biograph.

Radioimmunotherapy (RIT), an advanced radioisotope oncological therapy is gaining popularity. It combines radiation therapy and immunotherapy with the use of monoclonal antibodies which is paired with a radiotracer.[19] Pretargeted RIT (PRIT) is the most advanced and promising at the current time. Atworthy et al. demonstrated that PRIT yielded radiation localized to a tumor, which rivaled that of a directly radiolabelled antibody.[20]

Conclusions

Indeed Nuclear medicine is creating a future for personalized medicine and offers a unique opportunity for both early and accurate diagnosis and thus helps optimize the treatment and patient care.

It has very minimum radiation risks involved and minimal side effects which are usually allergic if any, which makes the benefits:risk ratio tremendous. It is safe, painless, non-invasive and cost effective.

The recent advancements in cell replacement therapy, gene therapy, radioimmunotherapy, PRIT, Fusion Imaging etc, emphasizes on techniques to trace the radiopharmaceutical and its biodistribution and retention in the body.

Thus to enhance the functioning of a radiopharmaceutical one should stride on developing new radiotracers or ligands and hybrid imaging systems which will combine both anatomic and physiological imaging. At the same time one should not forget that radiation is a two-edged weapon and should be used with utmost care.

Declaration of Interest

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