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Current Prospects in Diagnostic and Therapeutic Nuclear Medicine

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INTRODUCTION

Medicine is a rapidly changing science. Scientists are trying their best to develop newer, better and safer imaging and theraputic techniques to get the same or better information by cheaper and alternative means. The nuclear medicine is a amalgamation of basic science and clinical medicine and the strength of the modality is its ability to derive both functional and quantitative information about organ system. However, its weakness is the poor resolution i.e. poor quality images as compared to high-resolution images obtained from CT, MR and DSA etc.

Though, X-rays and gamma rays were discovered a century back, the pace of growth of nuclear medicine as a sub-speciality of medicine is disproportionately slow due to several reasons. First was the non-availability of suitable radiotracer till 1933. After discovery of artificial radioactivity and wide availability of tracer after World War II, this branch rapidly developed. The diagnostic use of radiotracer was handicapped due to non-availability of suitable imaging device. In 1951 and 1958 two remarskable discoveries, rectilinear scanner by Benidict Cassen and gamma camera by Hal Anger set a new pace for Nuclear Medicine. The rectilinear scanner decreased in popular due to slow mechanical movement of the detector, thus taking unusually long time for large organ imaging. Gamma camera was a good alternative but its potential could not be tapped till discovery of technetium in early 70s. Nuclear Medicine imaging became popular in late 70s and 80s. Tomographic techniques like US, CT and MR decreased its use further in late 80s. David Kuhl and Tor Pogossian developed Nuclear Medicine tomographic techniques such as SPECT and Position Emission Tomography, respectively. Now most of the Nuclear Medicine departments are equipped with SPECT and few with PET facility as well.

Diagnostic procedures in nuclear medicine are based on tracer kinetic principles. These can be broadly classified as follows :

1) In-vitro tests 2) In-vivo-Nonimaging procedures 3) In-vivo-Imaging

Procedures : a) Static imaging b) Dynamic imaging c) Gated imaging

1) In-vitro tests are mainly used in haematology practice. The most popular in-vitro test is the radioimmunoassay, which is universally practiced in medical profession. The other important tests are : (1) Autoradiography (2) Schillings test (3) Red cell mass estimation (4) Blood volume estimation (5) Red cell survival study (6) Platelet survival studies (7) Ferrokinetics (8) Radio respirometry (C-14 breath test) for malabsorbtion syndrome and widely used test for detection of H. Pylori in peptic ulcer disease. In the literature, there are many more procedures but few have survived over the years. The procedures are technically demanding and need certain degree of expertise for consistent results.

2) In-vivo non-imaging procedures : (i) The most popular and time tested procedure is Radio-active iodine uptake for the diagnosis of thyroid diseases. (ii) T4 Suppression test (iii) Perchlorate discharge Test (iv) Iodide perchlorate discharge test (v) GFR = (Glomerular Filtration Rate) and ERPF = (Effective Renal Plasma Flow) flow estimation (vi) Detection of hyperspleenism by spleen to cardiac uptake ratio estimation. The results are expressed as quantitative parameters and can be used in follow up for temporal comparisons. These are easy to perform with minimum laboratory equipments and technical expertise.

3) In-vivo imaging procedures : The modern day Nuclear Medicine is based on imaging procedures. The gamma camera is the work-horse of this speciality. This equipment can be used in planner or in tomographic mode. The number of detector head can vary from one to four. The widely available gamma camera is usually single headed, least expensive and highly versatile but time consuming and gives relatively poor quality image (due to inherent low sensitivity). As the number of detector heads increase the acquisition time decreases, count statistics improves thus giving better resolution and lower amount of tracer activity required thus, giving lower radiation dose to the patients. However, as the number of head increases arithmetically the cost of the equipment and the cost of the maintenance increase exponentially.

Apart from the detector heads in gamma camera, the other most important component is the computer (except the older generation analog cameras). Fortunately, over the years, the cost of the computers have decreased and the power to handle enormous data has increased indeed, it is the Nuclear medicine experts who started using computers for the first time in Medicine as early as 60s and paved the way for dedicated imaging computers in all branches of modern imaging.

The characteristics of an ideal radionuclide

There has been considerable discussion of the physical properties of an ideal radionuclide. Such an agent should be easily produced, readily available and inexpensive; and it should have high specific activity with no adverse reactions. Its physical half-life should be relatively short (i.e. only a few hours) and not longer than the time required for the agent to localize within the body and for imaging to be completed. The ideal gamma-emitting nuclide should decay by isomeric transition or electron capture without internal conversion. Those nuclides that decay with beta emission or significant conversion and those with longer physical half-lives are less desirable, since they result in a large radiation dose to the patient for the equivalent flux of externally detectable gamma photons. For most gamma cameras and scanning devices, the ideal nuclide should have a monoenergetic gamma emission of approximately 150 keV. At such an energy level, collimator septa may be extremely thin for higher counting efficiency, yet produce adequate attenuation. Furthermore, this energy level is high enough to permit demonstration of lesions at a considerable depth in tissues. The radionuclide that most closely approaches the characteristics of the ideal nuclide is technetium-99m, which will be discussed later.

In reality, no agent is ideal under all conditions. The agent of choice for the demonstration of a particular organ usually represents the best of several possible compromises. For example, ideal physical characteristics must often be sacrificed for biologic localizing properties. Some radionuclides, such as iodine-131, have been widely used in spite of their relatively poor physical properties because of their availability and chemical characteristics, which permit simple methods of labeling. Some compounds are so complex or difficult to label that the use of short-lived materials become impractical.

Imaging Procedures

a) The *static imaging* is performed either in spot views or in whole body mode depending on the need of the procedure. There is no count limitation however, the time limitation is the major factor. Pixel over saturation should be avoided and the acquisition time should be reasonably practical at the same time not compromising the quality of images. The best examples are bone scan, liver-spleen scan, renal cortical scan, thyroid scan, myocardiac infarct avid scan, ventilation/perfusion scans etc. These procedures need least expertise to acquire the images, but metionlousness is essential to get best results.

b) The *dynamic imaging* procedures are widely practiced in Nuclear Medicine. The dynamic word is in relation to temporal events i.e. the change of event in relation to time. From a routine renogram or to gall bladder ejection fraction calculation are all based on dynamic imaging technique. The event is recorded over a period of time after introduction of tracer into biological system and to see how the body is handling it. The sequence of recording of temporal events can vary from milli-seconds to hours. For example first pass studies needs to be recorded in milli-seconds, where as HIDA scan can go upto 24 hrs. Thus, continued or interval recording as required, is done for dynamic studies. After recording the events, through a screen interactive device (track ball, light pen marker or mouse) You have to draw a region of interest (ROI) or just identify a boundary inside which the computer through an edge detection algorithm marks the ROI. All the digitised images are passed through the ROI and time-activity histogram/curve are plotted. Then all the required parameters are derived from the time-activity-curve. The pattern and the area under the curve are frequently used to compare against the contralateral organ or compared over the period of time with the same organ. As the pixels are digitized the differential calculus applied to pixel can give the functional or parametric images. For pattern recognition different statistical methods like factor analysis, cluster analysis or discriminant analysis are applied to dynamic imaging data and resolve the subtle changes that is practically impossible to identify by human naked-eye observation. The cross talk or background scattering is the major problems with dynamic studies. The second most important problem is the count limitations, thus producing noisy images. The later can be partially solved by high sensitive detection methods or increasing the administered activity albeit within the permissible limit of the recommended dose. The former problem is a very difficult one. Lot of research has gone down to improve the methods of background correction. But only a partial success has been achieved yet. A great deal of hope is now being placed on the stochastic resonance method to augment a poor signal to noise ratio. Thus hoping to get good quality pictures in future.

c) *Gated Imaging* : If an organ is oscillating, it is very difficult to get good quality dynamic images. Fortunately bioelectricity can be recorded easily and the pattern is used for diagnosing medical problems. For example, heart is an oscillatory organ and its bio-electricity in the recorded form is called ECG. In ECG the tallest wave is "R Wave" which can be sensed by computer and used as a signal to open the gate for recording counts from that moment till the end of one cardiac cycle i.e. R to R interval. The next cardiac cycle is recorded in the same fashion; thus at the end of the thousand cycles one can have only one gaint cardiac cycle in computer memory. This recorded cycle can be replayed in cine mode and the actual heart best can be visualised in the monitor. Then all the techniques of dynamic image analyses can be applied and the time-activity curve can be derived. The functional images and the second derivatives parameter for the heart can be obtained easily. Principle of the same gating procedure can be applied for lungs as well, however its practical relevance is limited. The gating technique is efficient fully automated and operator friendly. However the atrio-ventricular overlaps and superimposition of great vessels create problems for proper analysis of the data. Gated-SPECT technique is being developed to overcome some of the problem of superimposition and background subtraction.

d) *Miscellaneous* : A score of new applications like radioimmunoscintigraphy, receptor imaging, absolute quantitation in metabolic imaging, perfusion imaging etc. are presently available, however, are beyond the scope of this discussion. The diagnostic Nuclear Medicine is becoming an exciting and challenging field with advent of receptor site visualization by modern PET and SPECT imaging.

THERAPEUTIC NUCLEAR MEDICINE

For more than 80 years, external beam radiotherapy, along with surgery and chemotherapy, has been a principal method in the triad of treatment modalities for cancer management. This treatment, however, results in irradiation of all tissue in the pathway of the radiation beam and thus normal tissues are also irradiated. Despite much improvement in linear accelerator collimation and multiple angles of irradiation (non-coplanar arc therapy), normal tissue toxicity in the local region limits treatment potential for many disease sites in the body. Sealed source or brachtherapy implants allow for targetting of target radiation in proximity to the lesions, but this form of radiotherapy is limited in practicalities of implant location (superficial or "cavity") and procedure invasiveness to normal tissues. In contrast to external beam radiotherapy, radiotherapy delivered via internal administration of radionuclides targeted via a tumor-seeking carrier has the allure of the "magic bullet." If a chemical form is found that specifically targets the undesired cell, specific therapy may be realized. Although the delivery method in practice, has been not without its problems. Treatment of diseases such as hyperthyroidism and thyroid cancer with radioiodine since the 1940s and polycythemia vera and leukemia with phosphorus (P-32) dating back to the 1930s (Saenger et al., 1979) exemplifies the history of routine treatment of some diseases via radionuclide therapy over several decades. As various small molecules and targeting proteins have been developed with specificity for malignant tissues, interest has been high in the development of an improved and broader base of targeted radiotherapy. Antibodies, in particular, by their nature have the potential of specific binding to an antigen, and if the antigen is found only on a cancer cell, antibodies carrying a therapy radionuclide may deliver specific, targeted radiotherapy. More recently, the finding of receptors on breast tumors, neuroendocrine tumors, and melanoma has thrown open the possibility of delivery of radiotherapy via radiolabeled peptide ligands. Molecular targeting raises the possibility of treating metastasis that are too small to be detected by standard diagnostic imaging. Such small lesions play an important role in relapse and mortality from metastatic cancer. The ability of these molecular-targeting methods to localise to the small lesions offer the opportunity to treat metastatic disease effectively. Have been used for the treatment bony metastasis, peritoneal tumor metastasis, and for the treatment of myeloproliferative disorders including polycythemia vera, certain leukemias, and essential thromocytosis. More recently, ^{89}Sr-chloride, ^{186}Re HEDP, and ^{153}Sm-EDTMP have been used for the therapy of bony pain from metastatic breast and prostatic carcinoma. Radiotherapy with these injected radionuclides has been effective in treating tumors because of the localization of the β emitting radionuclide within the tumor cell or within near proximity of the tumor cell. The success of the treatment depends on a high target-to-non target ratio of the radioisotope and on the residence time of the radionuclide within the tumor. These radiopharmaceuticals have a selectivity for tumor cells or, for the eroded bone adjacent to the tumor cells. The target binding is due to specific chemical properties that allow the radiopharmaceutical to bind. Except intracavitary uses, the radionuclide therapy is based on sound physico-chemical principles of tracer localisation. For example thyrocytes take radioiodine as the raw material for thyroid hormone synthesis, thus dying in the process. Similarly Sr-89/P-32 is taken up by osteoblasts for hydroxy apatite crystal formation and P-32 by proliferating haemopoietic cells for DNA synthesis and causing their self destruction. The third important point is the amount of radiation absorbed dose delivered to the organ or metastatic deposit is enormous as compared to the conventional radiotherapy.

Radioiodine for treatment of Graves' disease or toxic nodule has been the best example of a radionuclide targeting agent with a high target-to-non target ratio, rapid clearance of the unbound radioisotope, and a long residence time in the target. The result has been an effective therapy with little or no toxicity. The other targeted radiotherapy agents for systemic treatment of tumors have not had as high a therapeutic ratio and, in many cases, have not been as effective because of lower target to preferentially at or near tumor cells as compared to the non target cells. The tumor uptake in most intravenously injected radiolabeled antibody studies has been 1% or significantly less. Carrier molecules such as metaiodobenzylguanidine (MIBG) and somatostatin analogues have the advantage of being much smaller, which allows better tumor penetration. Additionally, they lack the problem of human anti-mouse or antihuman immune responses seen with the use of mouse-or human-derived monoclonal antibodies, potentially limiting the ability to repeat therapy. However, the slow rate of dose delivery over prolonged period, spares the healthy tissue surrounding the lesion, thus very little side effects by this mode of therapy.

PHYSICAL PROPERTIES OF THERAEUTIC RADIONUCLIDES

Several lists of rodionuclides suitable for therapy have been generated over the years (Fritzberg et al. 1988, Mausner and Srivstava 1984). A number of basic physical properties of these radionuclides are common to the group namely : A high non-penetrating to penetrating energy-abundance ratio (>0.5), particulate emissions, a physical half-life that the longer than the biological half-life, high specific activity of the final product and reasonable production methodology and availability. The basic theoretical considerations is presented in detail for beta-emitting radionuclides as they constitute main stay of therapeutic nuclear medicine. Humm et al (1986, 1987; Humm et al and Cobb, 1990), Howell et al. (1989), and Wheldon et al. (1991) have considered beta emitter potential with respect to energies, penetration or cell traversals, and appropriate size of tumor targets. A unique advantage of beta emitters over other therapeutic modalities (such as drugs and toxins) is that not every cell needs to be targeted to be killed. Thus, the transversals of cells by multiple beta particles results in enhanced killing by cross-fire. This result is efficient for lesions larger in diameter than the average path length. If the desired effect is eradication of micro-metastases in an adjuvant setting, a target cluster of tumor cells may range from several thousand cells (0.1mm) to 10^5 (1 mm) cells.

A medium-energy beta emmitter, such as ^{131}I, has 17% of its energy absorbed in a cluster of cells of 0.2 mm diameter, whereas only 1.5% of the high-energy beta emitter ^{90}Y is absorbed. For a 1mm cluster, the corresponding absorbed percentages are 54% for ^{131}I and 10% for ^{90}Y (Humm 1986). This results in escape of most of ^{90}Y from micro-metastasis to give potential non-target toxicity. Detailed analysis of these considerations by Wheldon and co-workers in 1991 suggest that ^{131}I or similar energy radionuclides be used for tumors of $10^{4.5}$ to $10^{7.5}$ cells and ^{90}Y for tumors of 10^8 to 10^{11} cells. It is of interest that detectability of tumors and metastasis with standard imaging modalities is on the order of 10^9 cells, or about 1 cm diameter.

Humm (1986) has classified beta emitting radionuclides as low-range (mean range <200 micrometer), medium-range (mean range, 200 micrometer to < 1mm) and high range (mean range>1mm). Some examples are as follows :

* Low range : europium (169 Eu), lutetium (177 Lu)

* Medium range : scandium (^{47}Sc), copper (^{67}Cu), iodine (^{131}I), samarium (^{153}Sm), rhenium (^{186}Re)

Physical properties of selected Therapeutic Radionuclides

Radionuclide	Half-life (hrs)	E_{max} Beta (meV)	Mean Range (mm)	Imaging Gamma energy in KeV (%Abundance)
^{32}P	342	1.71	1.85	---
^{67}Cu	62	0.57	0.27	185(49%)
^{90}Y	64	2.27	2.76	---
^{131}I	193	0.61	0.4	364(81%)
^{153}Sm	47	0.8	0.53	103(28%)
^{177}Lu	162	0.5	0.28	208(11%)
^{186}Re	89	1.07	0.92	137(9%)
^{188}Re	50	2.12	2.43	155(15%)

* Long range : phosphorus (^{32}P), rhenium (^{188}Re), yttrium (^{90}Y)

The physical properties of radionuclides of interest that vary from low means range of 0.28 mm for ^{177} Lu to 2.76 mm for (^{90}Y) are listed in the following table.

External Monitoring

Penetrating gamma radiation is emitted by many therapeutic radionuclides. This property enables imaging of the biodistribution of the radiotracer and facilitates pharmacokinetic studies. When the gamma emissions are of appropriate energies (between 100-200 KeV), the target activity and other normal tissue uptake and retention of radioactivity can be measured as a function of time after injection of the radiopharmaceutical. This allows dosimetry estimates to be made on the actual therapeutic dose rather than relying on similarities to the behaviour of diagnostic imaging agents. The radionuclides should emit a relatively low abundance of gamma photons so that the absorbed dose contributed to normal tissues is not significant. On the other hand, ^{32}P and ^{90}Y lack gamma emission. Although their high energy beta emissions result in penetrating *bremsstrahlung* radiation, the broad energy spectrum of high energy photons limits the spatial resolution that can be obtained and results in poor images of radiotracer distribution.

Preparation of the patient before therapy

A suitable tracer study should be performed to give an idea of the distribution and uptake pattern of the tracer and from this dosimetry can be obtained. The blood or marrow dose is most important dose limitting factor. Thus, special attention should be given to that while administering the radionuclide therapy. As it is expected after therapy these shall be tissue oedema, any critical organ must be adequately protected. For example in a patient with thyroid cancer and tracheal/laryngeal infiltration likely to go for respiratory distress. So a prophylate tracheostomy is advocated, similarly, patients with impending paraplegia should be given local radiotherapy prior to 1-131 therapy in metastatic CA thyroid. In an elder thyrotoxic patient adequate control of hyperthyroidism is required before giving 1-131 therapy.

The route of administration : Intraoral, intravenous, Intraarterial or Intracavitary

Limitations of Radionuclide of Therapy : The major limitations of radionuclide therapy are as follows : i) The patient becomes a radioactive source and if the radionuclide produces energetic gamma rays alongwith particulate emission, needs strict isolation for many days. ii) Each type of tissue needs a unique radionuclide thus an array of radionuclides are needed to cover large number of diseases/organs. Whereas a Telecobalt unit can treat most of the tissues with the same source of radiation. iii) The radioactive waste disposal become problem. Needs special care to handle the wastes with due permission from the regulatory bodies of the nation as well as local authorities. iv) You have to have trained and dedicated staff to cater the need of large volume of patients with isolation rooms specially designed and ear marked exclusively for this therapy only. v) The limited availability of the common radionuclides like 1-131/P-32 and prohibitively expensive radionuclides like Sr-89 has really handicapped the Nuclear Physician to treat more number of patients by this therapeutic modality.

The vast therapeutic potential of nuclear medicine is as yet untapped. Exciting new applications include palliative therapy of bone metastasis of neuroectodermal and somatostatin expressing tumors.

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