Azadi ka Amrit Mahotsav ISAS Webinar Series: A few Excerpts

Role of Radiopharmaceuticals in diagnosis and therapy

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Abstract: Radiopharmaceutical products are inorganic, organic and biological compounds labelled with radionuclides which are used for diagnostic and therapeutic purposes. The lecture covers some basic principles of radiopharmaceuticals and its applications in health care. Use of Positron Emission Tomography, static and dynamic imaging , in-vivo and in-vitro methods for detection of thyroiditis are discussed in brief followed by use of radiopharmaceuticals in radiation therapy. The role of radiopharmaceuticals in covid treatment is also highlighted. Brief description of the work carried out by our research group in detection of thyroiditis in pregnant women and children, and synthesis of I-125 brachytherapy source for the treatment of retinoblastoma is followed by the precautions to be taken while using the radiopharmaceuticals in diagnosis and therapy.

Introduction: When the word "radioactivity" is heard, most of the people are afraid of it as they remember Hiroshima, Nagasaki, and other nuclear accidents; a destructive side of it! On the other hand, its positive side depicts large number of peaceful applications, most of them being in the field of medicine. The present article gives an overview of radiopharmaceuticals and their applications in diagnosis and therapy.

Historical Background: The golden age of nuclear and radiation chemistry started with the discovery of X-rays on 8th July 1895 by William Rontgen. Just 114 days after that Becquerel invented the phenomenon of radioactivity, the name "Radioactivity" being coined by Marie and Pierre Curie who discovered Po and Ra in 1898. All of them were conferred with Nobel prize. Discovery of Artificial radioactivity by Irene and Frederic Joliot curie in 1934 made it possible to synthesize large number of radioisotopes which has found applications in almost every branch of science. Few more discoveries in this field were that of cyclotron (Lawrence), Nuclear fission (Hahn and Strassman), Nuclear Reactor (Fermi and co-workers), radioisotope tagging(Hevesy).

Nuclear Medicine: Nuclear medicine is a special branch of medicine, the origin of which lies in the discovery of X-ray and artificial radioactivity. In 1946, radioiodine was used to treat the thyroid cancer. In the decade of 1950s, use of nuclear medicines was started at a larger scale. In 1960s, nuclear medicine was recognized as a special branch while in the decade of 1970s, use of nuclear medicines to study other organs was started and, in the decade of 1980s, first time nuclear medicines were used to study heart diseases.

Progress of Nuclear medicine in India: Dr. Homi Bhabha played very important role in starting nuclear medicine branch in India. In 1960, a research grant was made available at Department of Atomic Energy and in 1963, radiation medicine Centre was started at Tata memorial hospital. Dr. Ernest Lawrence, N.L. provided many equipments. Bhabha Atomic Research Centre and Board of Research in Isotope Technology played a major role in the progress of nuclear medicine branch in India.There are AERB approved (as on 2.12.20) 349 nuclear medicine centers in India out of which 49 are in Maharashtra and 9 in Pune.

Radiopharmaceuticals: The inorganic/organic compound containing radiotracer when used for diagnosis and therapy, it is known as a radiopharmaceutical which gives anatomical as well as physiological information of the organ under study. It can be designed by considering its preferred localization and biological function in the organ. The radiopharmaceutical dose can be planned depending on its physical and biological half-life as well as benefit/risk ratio. Its effective half life should not exceed 1.5 times the test duration. Depending on its use, type of radiations are selected. Usually gamma emitting isotopes with an energy of 0.1-.25 MeV

are preferred. Now a days targeted therapy is used to avoid radiation dose to surrounding tissues.

Some of the commonly used radiotracers, their chemical form and uses are: **Tc-99m** (Sodium pertechnetate): Brain, blood pool imaging, **I-131**(Sodium iodide):Thyroid diagnosis and therapy, **Xe-133** (gas):Pulmonary inhalation imaging, cerebral blood flow studies,**Tl-201** (thallous chloride) :myocardial imaging, **Ga-67** (Gallium citrate): Tumor imaging.

Various units used for measuring the radiation dose[1] are Curie (Ci), Rad (r), Rontgen(R), Relative Biological Effectiveness (RBE), Rontgen Equivalent Mammal (REM) and Sievert (Sv).

Radionuclide generators:

These are used to extract relatively short lived radioisotope from its parent nuclide. Most of the nuclear medicine centres use technetium generator. There is a transient equilibrium between ^{99}Mo ($t_{1/2}$ = 2.7 d) and ^{99m}Tc ($t_{1/2}$ = 6 h). Hence one can extract ^{99m}Tc from loaded ^{99}Mo in the generator when it reaches a maximum activity. Growth and decay of ^{99m}Tc is a continuous process and one can extract it repeatedly after certain interval of time, just like milking a cow after certain time period. The generator essentially consists of alumina column adsorbed with ^{99}Mo wherein its decay results in ^{99m}Tc . ^{99m}Tc can be extracted from this column using sterilized saline solution (Fig.1).

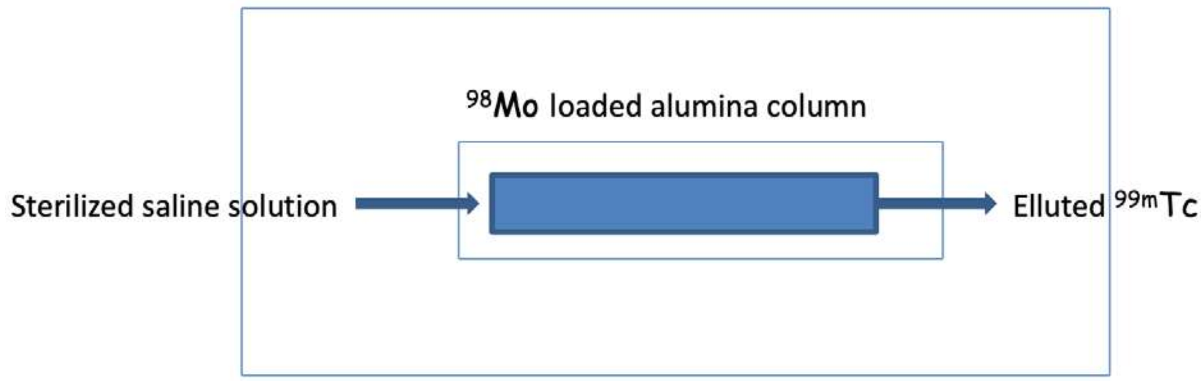

Fig.1 A schematic diagram of Technetium Generator

Radiopharmaceuticals for Diagnosis: In vivo diagnosis: For diagnosing a patient by in-vivo method, radiopharmaceutical is either injected into the patient or given orally/ by inhalation depending on the purpose. NaI(Tl) detector is used as gamma camera for monitoring gamma rays emitted which can be further analysed to get the required information about the diseased organ. Uptake of radiopharmaceutical will be different for normal and diseased tissues. Increased uptake (eg. ^{99m} Tc in bone cancer) is referred to as 'hot spot' while decreased uptake (eg.^{204}Tl in heart scan) is referred as 'cold spot'

The half-life of radioisotope used in nuclear imaging must be sufficiently long to monitor the function of organ but it should not be too long to avoid further damage to the tissue. Its gamma energy must be sufficient for penetrating the tissue.

Positron emission tomography[2] (PET)

PET is one of the most powerful technique used for imaging the organs. It is mainly used for detection of cancer and to study spread of cancer and to review the effectiveness of radiation therapy. Positron emitting radioisotope (e.g. F-18 in the form of FDG) is injected into the patient. Emitted positron loses its kinetic energy during interaction with surrounding atoms and combines with the surrounding electron. This leads into an annihilation process resulting into two gamma photons (each of 511 keV energy) exactly in opposite directions (180º to each other). Thus, three dimensional image of the organ under study can be obtained. F-18 fluro deoxy glucose(FDG) acts as a scanning agent during imaging process. It acts like glucose and gets transported into the cells. Malignant tumours have increased glycolysis (hence increased uptake of FDG) resulting into hot spot in the image.

Some of the radioisotopes used for PET are: Ga-88($t_{1/2}$ = 68 min), N-13 ($t_{1/2}$ = 10 min), C-11 ($t_{1/2}$ = 20.4 min) and F-18 (1 $t_{1/2}$ = 10 min). Out of these F-18 is most widely used.

Static and dynamic imaging: The imaging techniques are classified as static and dynamic.

Static imaging: In static imaging, radiopharmaceutical is first injected, and further imaging is carried out once the radiation is taken up by the organ. PET is the example of static imaging and usually used for brain, bone, and lung studies.

Dynamic imaging: In dynamic imaging, uptake of radiopharmaceutical in the organ is measured as a function of time after its injection and usually used for heart and kidney functioning.

Renogram: In order to study the function of a diseased kidney, renograms (dynamic images of kidney) are carried out. The tracer [MAG-3(Tc-99m)] is injected into the patient which will be taken up by the kidney from the blood stream and gets concentrated in it. Continuous uptake and decay of radiotracer is studied as a function of time for about 20 min., for every few seconds, using gamma camera. Normal renogram shows initial uptake followed by decay of tracer. However, diseased one shows different profile showing ups and downs in the curve depending on the extent of damage.

Thyroiditis: Thyroid is the critical organ for iodine and it plays very important role in our growth and metabolism. Iodine consumed by us gets accumulated in this gland. The adequate intake of iodine is in the range of 50-200 μg d^{-1}, and The Recommended Dietary Allowance (RDA) of India is 150 μg d^{-1}. Excess or less iodine uptake by the body results into hyper or hypothyroidism respectively, the condition can be diagnosed using I-131 radiotracer. In a recent survey it has been reported that, in India, out of 324 districts surveyed, 264 have been found to be endemic for iodine deficiency disorders (IDD).

In-vivo diagnosis of thyroiditis [1]: I-131(10 μCi) is added to the juice and orally administered to the patient. I-131 reaches the thyroid gland, gets accumulated and decays.

Gamma activity of the radiotracer is measured at interval of 1h at about 20 cm away from the patient. One can diagnose hyper/hypo throidism from the following Fig.(Fig 2). Once diagnosed, I-131 (200 μCi)can be used for therapy of hyper thyroiditis.

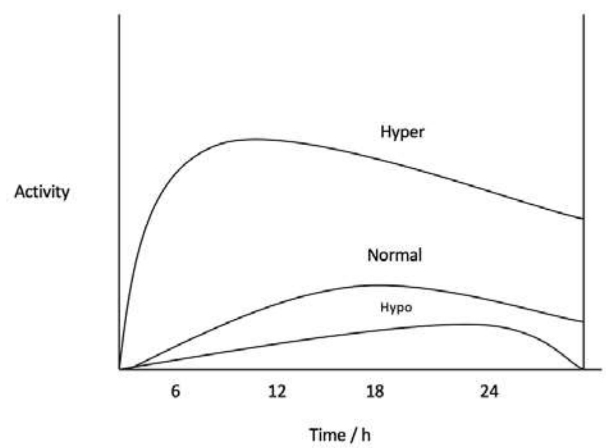

Fig.2 Thyroid condition

In vitro diagnosis of thyroiditis: The technique of Radio Immuno Assay (RIA) is used for the in-vitro diagnosis of thyroiditis. Antigen-Antibody reaction in this assay can be shown as follows:

(Antigen) + (Labelled antigen) + (Antibody)

→ (Antigen-Antibody complex) + (labelled Antigen-Antibody complex) + Free labelled antigen + Antibody

Antigen (Thyroid hormone) can be measured by measuring radioactivity of bound antigen antibody complex. The technique is highly sensitive and one can measure ng concentration also.

Work carried out by our research group[3]

Children and pregnant women are more prone to thyroiditis. Hence, we selected pregnant women and children from Pune city and nearby area for the studies. Serum samples were analyzed for thyroid hormones. Research grant was provided by BCUD, SPPU and UGC UPE phase II.

RIA kits from BRIT, Mumbai were used to estimate thyroid hormone concentrations. The thyroid hormone, RIA kit used and normal concentration range of these hormones are listed in following Table (Table 1).

Table 1 RIA of thyroid hormones

Thyroid hormone	RIA kit	Normal range of thyroid hormone
T3	**MAG 3**	0.7 to 2.1 ng/mL
T4	**BRIA MAG 4**	55-135 ng/mL
hTSH	**IRMAK-9**	0.17 to 4.05 ng/mL

Our results showed that out of 243 Pregnant women, 128 Were prone to hypothyroidism and out of 172 children, 65 Were prone to hypothyroidism.

Radiation therapy: In order to treat the cancer patients tiny sealed gamma source is used which delivers the desired dose to the patient through collimator. When the source is kept at certain distance from the patient, it is termed as teletherapy and when the source is kept close to affected organ, it is called as brachytherapy. Most commonly used gamma sources for radiation therapy are: Co-60 ($t_{1/2}$ =5.27y), Cs-137 ($t_{1/2}$ =30 y) I -125 ($t_{1/2}$ = 60 d)

Requirements of Sources for their Use in Radiotherapy[4]:

(1) Solid and Non-leachable (Insoluble) Matrix (2) Stability against Heat and Radiation

(3) Higher Specific Activity (4) Smaller Source Size

(5) Inertness towards Encapsulating Material (6) Low Leachability

(7) Uniformity of Activity within Source Core (8) Activity Variations within ± 10%.

(9) Ease of Source Preparation (10) Economic Viability

Work carried out by our research group[5,6]

We had prepared I-125 brachytherapy source in association with radiopharmaceuticals division, BARC. Initially, 100 MBq of I-125 was allowed to adsorb on Pd - Ag rod . It was then encapsulated in a tiny titanium capsule(0.8 mm diameter and 4.75 mm length). Brachytherapy sources thus prepared were then used for the cancer treatment (retinoblastoma and prostate cancer) [4-6] at different nuclear medicine centres.

Use of radiopharmaceuticals in diagnosis of Covid 19: During pandemic period of Covid19, Computational Tomography (CT) technique was used for examining the chest for the detection and monitoring of pneumonia induced by Covid 19. The technique gives three-dimensional image which can track the location of the organ affected and progression of the disease.

Another technique which was used to examine covid 19 patient was PET. The technique was used for few patients before the formal outbreak of covid-19 using F-18 radiotracer which indicated the lymph node involvement. The technique was used at different nuclear medicine centers during pandemic period. Asymptomatic patients also showed Covid 19 induced pneumonia during PET examination. PET technique played an important role in identifying the prevalence of COVID-19 among high-risk, asymptomatic patients.

Covid -19 therapy using radiopharmaceuticals: One of the first study was carried out by researchers at Emory University Hospital. Few patients with Covid 19 having severe pneumonia were treated with 1.5 Gy gamma radiation dose applied to both the lungs[7]. Most of them showed rapid recovery and there was no adverse effect of radiations. Similar results were observed at the AIIMS facility in New Delhi, two severely ill patients were given 0.7 Gy to the lungs and they were recovered. More patients were then treated. Now a days many countries are using this therapy for treating the covid 19 patients

Probable effects observed after radiation therapy: Generally, effects are seen after second or third cycle of radiation therapy. Fatigue, vomiting, hair loss are some of the common effects. Probable effects after radiation therapy on some of the organs are:

- Brain: Fatigue, vomiting, hair loss, dry skin, headache, eyesight is affected
- Breast: fatigue, hair loss, swelling, skin gets affected
- Chest: Fatigue, hair loss dry skin, throat ache, breathing problem

Precautions to be taken while using the radiopharmaceuticals: As an example, precautions while I-131 is used for diagnosis and therapy of thyroid are described

- Do not consume food which contains iodine before few weeks of the treatment
- Consumption of radioiodine decreases WBC hence the person should not come in contact with the patient having infectious disease
- Drink more water after taking the radioiodine dose
- Person taking the treatment should avoid the contact with others. His clothes and other belongings are to be kept separate
- Flush twice after using the toilet
- Patient must be hospitalized unless his radiation dose becomes less than 5 mrem/h
- Floor of the Patient’s room must be covered with plastic or absorbing material. Similarly other objects also to be covered
- RSO should see that radioactivity should decrease to less than 200dpm/100 square cm before room is allotted to another patient

Conclusion:

Radiopharmaceuticals play very important role in health care as they are effectively used in diagnosis and therapy of various diseases

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Brief Bio-sketch of Dr. Nilima S. Rajurkar

Dr. (Mrs.) Nilima Rajurkar is Former Professor and Head of the Department of Chemistry and Former Head, Department of Environmental Science at Savitribai Phule Pune University with a teaching experience of more than 40 years. She is a Fellow of Maharashtra Academy of Sciences and has been working in multidisciplinary areas such as Nuclear and Radiation Chemistry, Electrochemistry, neutron activation analysis, Environmental pollution, wastewater treatment, medicinal plant chemistry, synthesis of ayurvedic bhasma, radiopharmaceuticals, public health etc. Through her career, she has guided 16 students for M. Phil and 30 students for Ph.D. degree from various parts of India and Abroad. She has more than 200 research publications in National and International journals. She acted as the Editor of International journal “Clean-Soil Air and Water” of Wiley Blackwell and also as

peer team member of NAAC. International Biographical Research Centre at Cambridge, UK has listed her among the “Leading Scientists in Nuclear Chemistry” in 2009 and Indian Council of Chemists conferred her with “Prof. Kaza Somshekhara Rao Award ”for Best Women Scientist in Chemistry” in 2014.She has written a book “Nuclear chemistry through problems” with Prof. H .J. Arnikar and she is also a co-author of a book on “Science and Technology” for competitive exam students. She was involved in preparing video films on ‘Radioactivity’ and lectures on ‘Environmental Science’ for UGC countrywide classroom in association with EMRC, Pune. She visited various countries for invited talks and conferences and also organized number of National and International conferences, workshops and seminars. She was the Vice President of “Indian Association of Nuclear Chemists and Allied Scientists”, EC Member of Indian Science Congress”, “Convener, “Indian Women Scientists’ Association, Pune branch” and Vice President of “Marathi Vidnyan Parishad, Pune Vibhag”. Presently, she is Chairperson of “Indian Society of Analytical Scientists, Pune Chapter” and Editor of the ”Journal of ISAS”. She is a member of number of scientific societies through which she is actively involved in science popularization program