Asian Journal of Chemistry;   Vol. 24, No. 12 (2012), 5450-5452

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Role of Radiopharmaceuticals in Diagnosis and Therapy†

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AJC-11664

The lecture begins with the glimpses of development of the subject of radiochemistry. This is followed by synthesis of radioisotopes and the various units used for measurement of radiations. The major uses of radioisotopes in medical field include diagnosis, therapy and sterilization. A radiopharmaceutical is a radioactive compound used for the diagnosis and therapeutic treatment of various human diseases. Radiopharmaceutical products include inorganic compounds, organic compounds, peptides, proteins and monoclonal antibodies, which are labeled with radionuclides with half-lives varying from a few minutes to several days. The use of radiopharmaceutical gives both anatomical and physiological information of the organ. Its designing is based on the preferential localization of radiopharmaceutical in a given organ or participation of it in the physiologic function of the organ. The general principles for use of radiopharmaceuticals and their properties for ideal diagnostic and therapeutic purposes are discussed in brief. The principle of radionuclide generator with an example of technetium generator is described. The applications of radiopharmaceuticals in diagnosis of various diseases using Positron emission tomography, static and dynamic imaging are discussed. Radiation therapy is a technique, which is widely used for the treatment of cancer by delivering radiation dose to the affected lesion with the help of tiny sealed radioactive sources. In teletherapy the source is kept away from the lesion and radiation beam is directed to the affected part with the help of collimators while in brachytherapy the tiny radiation sources are deployed for the treatment of cancer and benign diseases by placing them in the close proximity of affected lesion. Preparation of I-125 brachytherapy source for the treatment of retinoblastoma is discussed in brief at the end of lecture.

Key Words: Radiopharmaceuticals, Radiation therapy, Thyroiditis, Retinoblastoma.

Glimpses of development of radiochemistry: The golden era of number of discoveries related to radioactivity in particular and radiochemistry in general started in the last decade of nineteenth century. It began with the accidental discovery of X-rays by William Rontgen in 1895 followed by discovery of radioactivity phenomenon by Henry Becquerel in 1896. The phenomenon was christened as radioactivity by Marie Curie and Pierre Curie who were discoverer of Po and Ra an 1898. All these scientists were recipient of Nobel prizes, Rontgen in 1901 and Curies together with Becquerel in 1903. There were twelve more Nobel prizes in this field. The list of discoveries in the field of radioactivity is given in the following Table-1.

All these discoveries painted such a vast canvas of human endeavor that not a single branch of science is left untouched. After the discovery of artificial radioactivity number of radioisotopes were synthesized by using neutrons and charge particles. Some of the examples are given below.

TABLE-1
DISCOVERIES IN THE FIELD OF RADIOACTIVITY

Name of the Scientist	Discovery	Year
William Rontgen	X-rays	1895
Henry Becquerel	Radioactivity	1896
Marie and Pierre Curie	Po	1898
Marie and Pierre Curie	Ra	1898
George Hevesy	Radioisotope tagging	1913
Ernest Orlando Lawrence	Cyclotron	1930
Frederic and Irene Joliot-Curie	Artificial Radioactivity	1934
Otto Hahn and Strasman	Nuclear Fission	1939
Fermi & coworkers	Nuclear Reactor	1942

Synthesis of radioisotopes

Bombardment with neutrons

$$^{55}Mn(n, \gamma)\ ^{56}Mn\ (t_{1/2} = 2.58\ h;\ En = \sim 0.1\ eV)$$

Bombardment with charge particles

$$^{24}Mg\ (d,\alpha)\ ^{22}Na\ (t_{1/2} = 2.6\ y;\ Ed = 8.5\ MeV)$$

Decay of radioisotopes

$$^{130}Te\ (n, \gamma)\ ^{131}Te \rightarrow\ ^{131}I\ (t_{1/2} = 8.4\ days)$$

†Presented as invited lecture to the International Conference on Global Trends in Pure and Applied Chemical Sciences, 3-4 March, 2012; Udaipur, India

The number of radioisotopes synthesized in 1937 were 200, in 1944 it was 450 and presently more than 2000 radioisopes are being synthesized. The survey of aaplications of radioisotopes in different fields indicate that maximum use is in the field of medicines (57 %).

Radiopharmaceuticals: A radiopharmaceutical is a radioactive compound used for the diagnosis and therapeutic treatment of various human diseases. The use of radiopharmaceutical gives both anatomical and physiological information of the organ. Its designing is based on the preferential localization of radiopharmaceutical in a given organ or participation of it in the physiologic function of the organ.

General principles of use of radiopharmaceuticals: (1) Radiopharmaceutical Provides important information about the disease which could not be obtained in any other way; (2) Risk/benefit ratio decides the dosage of a radiopharmaceutical; (3) Optimum time of radiopharmaceutical in the body is of importance; (4) Type of radiation emitted by the radionuclide is selected depending on the purpose of its use; (5) Radioactive as well as biological half-life is to be taken into consideration.

Before looking into actual applications of radiopharmaceuticals we have to consider some important units of measuring radiations. These are[1]:Curie: 3.7×10^{10} dps; Bq = 1dps, Rad: Absorption of 100 erg/g, Gray: 1 Gy = 100 rads, Rontgen: absorption of such a dose that would produce in 1 cc of dry air 1 esu electricity, relative biological effectiveness (RBE):1 for X and γ-rays, 2.5 for thermal neutrons,10 for α-particles, fast neutrons and protons, roentgen equivalent mammal (REM): RBE × rads, Sievert : RBE × grays

The properties of ideal diagnostic radiopharmaceutical are[2]: It must be a pure gamma emitter with energy between 100 and 250 keV. Its effective half life must be 1.5 times the test duration. While using it, target: non target raio should be high. There should be minimal radiation dose to patient and nuclear medicine personnel. Patient safety is of utmost importance. The radiopharmaceutical should be readily available and economic. If it is manufactured in house, preparation should be simple and quality control is to be performed.

Radionuclide generators: Radionuclide generators[3] allow to separate chemically short-lived radioactive daughter nuclei with good characteristics for medical imaging from long-lived radioactive parent nuclei. Typical techniques used are chromatographic absorption, distillation or phase separation. This method is in particular applied for the separation of the rather short-lived ^{99m}Tc ($t_{1/2}$ = 6 h) from the long lived ^{99}Mo ($t_{1/2}$ = 2.7 d) radioisotope.

Applying the radioactive decay law the growth of activity of the daughter nuclei A_2 with respect of the initial activity of the mother nucleus A_1^0 can be expressed in terms of their respective decay constants λ_2 and λ_2 with $\lambda_2 >> \lambda_1$ (Fig. 1).

A typical radionuclide generator is shown in Fig. 2

Radiopharmaceuticals for Diagnosis: *In vivo* diagnosis: For *in vivo* diagnosis, radiopharmaceutical is introduced into the system of a living patient either orally or by injection/inhalation and the gamma rays emitted by radiopharmaceuticals are monitored to provide the desired information using Gamma camera: NaI (Tl) detector. Diseased portion of an organ may differ from normal tissue in their tendency to take up radiopharmaceutical. Increased uptake gives hot spots while reduced uptake gives cold spots. Thus Tc-99 m when used to dignose bone cancer, it gives hot spots while Tl-204 when used for heart scan, the damaged portion gives cold spots.

$$A_2(t) = A_1^0 \cdot [e^{-\lambda_1 \cdot t} - e^{-\lambda_2 \cdot t}]$$

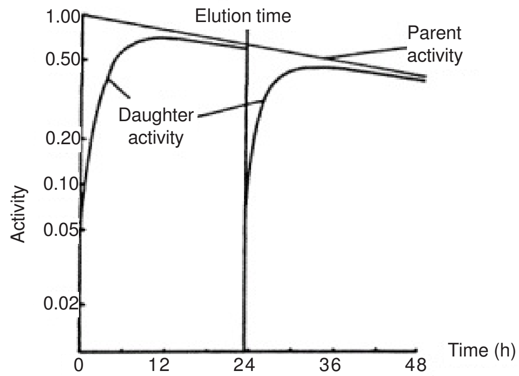

Fig. 1. Typical growth decay curve of daughter

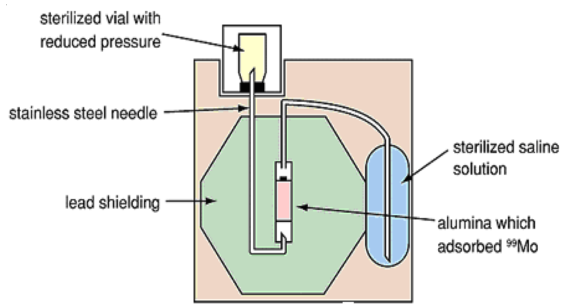

Fig. 2. A typical Technetium generator

The choice of the appropriate radioisotope for nuclear imaging is dictated by the physical characteristics of the radioisotope: It should have a suitable physical half-life; long enough for monitoring the physiological organ functions to be studied, but not too long to avoid long term radiation effects. It should decay *via* photo emission to minimize absorption effects in body tissue. Gamma energy must be sufficient to penetrate body tissue with minimal attenuation. Decay product should have minimal short-lived activity.

Positron emission tomography[4]: This is most widely used imaging technique, which gives three dimensional image. In this technique a positron emitter is used. During positron emission process, a proton inside the nucleus turns into a neutron and positron and neutrino are emitted. The positron gradually loses its kinetic energy during interaction with surrounding atoms and combines with an surrounding electron. Then positron and electron are converted to the gamma photons which are emitted at 180º to each other, each with energy 511 keV (annihilation). Hence it it is possible to take three dimensional image of diseased organ. 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.

Thyroiditis: Most of the iodine taken from food is accumulated in thyroid glands, which plays a vital role in the well being as it controls growth and metabolism. In some people gland becomes over active (hyper thyroidiis) and in some people gland becomes sluggish (hypo thyroiditis). However, both the conditions are unhealthy and lead to serious consequences. These conditions can be detected and treated with the help of I-131 radioisotope.

In-vivo diagnosis of thyroiditis

Diagnosis: A glass of orange juice containing 10 micro curie of I-131 is given to the patient. The counting of gamma activity emitted by patient's thyroid is measured at a distance of 20 cm from the thyroid and the counts are compared with dummy thyroid. The counts are measured after every 1 h. The condition of thyroiditis can be seen from following curves[1] (Fig. 3).

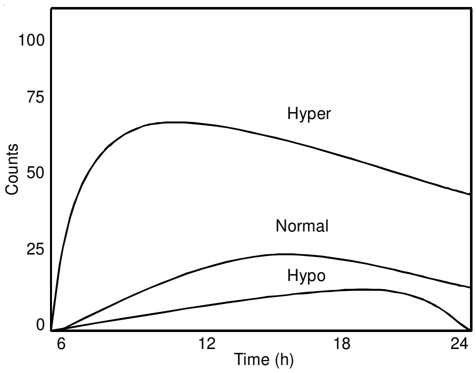

Fig. 3 Dignosis of thyroiditis

Hyperthyroiditis can be treated by giving 200 microcurie of I-131.

***In vitro* diagnosis of thyroiditis:** This can be done by using radioimmuno assay technique. In this technique, an immune reaction [Antigen-Antibody reaction] is used to estimate a ligand

$$Ag + Ag^* + Ab \rightarrow AgAb + Ag^*Ab + Ag + Ab^*$$

[Ag : ligand to be measured ; Ag* radiolabelled ligand]

unbound Ag* and Ag are washed out and radioactivity of bound residue is measured. The ligand concentration is inversely related to radioactivity.

Methodology for RIA: Known amounts of the test sample + labelled antigen are added into the microtitre wells and incubated to allow the reaction to reach completion, then supernatant solution is decanted and contents of the well are to be washed to remove all unbound antigens. Radioactivity remaining in the microtitre wells is to be measured by a GM counter/scintillation counter and it is inversely correlated with the concentration of antigens in the test sample. It is very sensitive to very low concentration of antigens.

In our laboratory we have used RIA kits supplied by Board of Research in Isotope Technology, Vashi, Mumbai for estimating T3 T4 and TSH harmones to diagnose thyroiditis in pregnant women. Following kits were used:

BRIA MAG 3 RIA kit for total triiodothyronine T3 (magnetic particle separation system): Normal range of T3 : 0.7 to 2.1 ng/mL; BRIA MAG 4 RIA kit for total thyroxine T4; Normal range of T4 : 55-135 ng/mL; IRMAK-9 RIA kit for human throid stimulating harmone hTSH; Normal range of TSH : 0.17 to 4.05 ng/mL.

50 pregnant women of different trimester were selected for examination of iodine deficiency disorder. Analysis of data revealed that 15 women showed T3 level < 0.7 ng/mL, T4 level < 55 ng/mL and TSH < 0.15 ng/mL, which are indicator of hypothyroidism and 2 women showed T3 level > 2.1 ng/mL, T4 level > 135 ng/mL and TSH > 5 ng/mL, *i.e.* indicator of hyperthyroidism.

Radiation therapy: Radiation therapy is a technique which is widely used for the treatment of cancer by delivering radiation dose to the affected lesion with the help of tiny sealed radioactive sources. In teletherapy the source is kept away from the lesion and radiation beam is directed to the affected part with the help of collimators while in brachytherapy the tiny radiation sources are deployed for the treatment of cancer and benign diseases by placing them in the close proximity of affected lesion. The radiation sources used for cancer therapy are: Co-60 ($t_{1/2}$ =5.27y), Cs-137 ($t_{1/2}$ =30 y) I -125 (6 $t_{1/2}$ = 60 d).

In collaboration with radiopharmaceuticals division of BARC, Mumbai, we had prepared I-125 radiation plaque for the treatment of retinoblastoma and prostate cancer[2,4,5], the details of which are given below:

I-125: Half life: 60 days; Energy: 28 keV; Adsorption of -100 MBq of I-125 on Pd - Ag rod; Encapsulation in tiny titanium capsule of size 0.8 mm diameter and 4.75 mm length. The capsules are shown in Fig. 4.

Fig. 4. Radiation plaque of I-125

Conclusion

Radiopharmaceuticals can be used in diagnosis and therapy for large number of diseases and number of applications are still increasing.

ACKNOWLEDGEMENTS

Author is thankful to Dr. Meera Venkatesh, Sanjay Saxena from Radiopharmaceuticals Division, BARC, Mumbai, Dr. N. Shivaprasad from BRIT, Vashi, Mumbai and Neeta Zatakia from Department of Environmental Science, Pune University for extending their help in carrying out some of the experiments. Author is also thankful to BCUD, Pune University for financial assistance.

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