Medical Radioisotopes for the Next Century

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SUMMARY. Radioisotopes are widely used in medicine (Nuclear Medicine) for diagnosis, palliation and therapy of heart disease, cancer, muscoskeletal and neurological conditions. The radioisotopes used are both reactor and cyclotron produced. The utilisation is currently growing and is expected to continue to grow over the next 10-20 years. The combination of radioisotope and delivery vehicle can be designed to meet the intended end use.

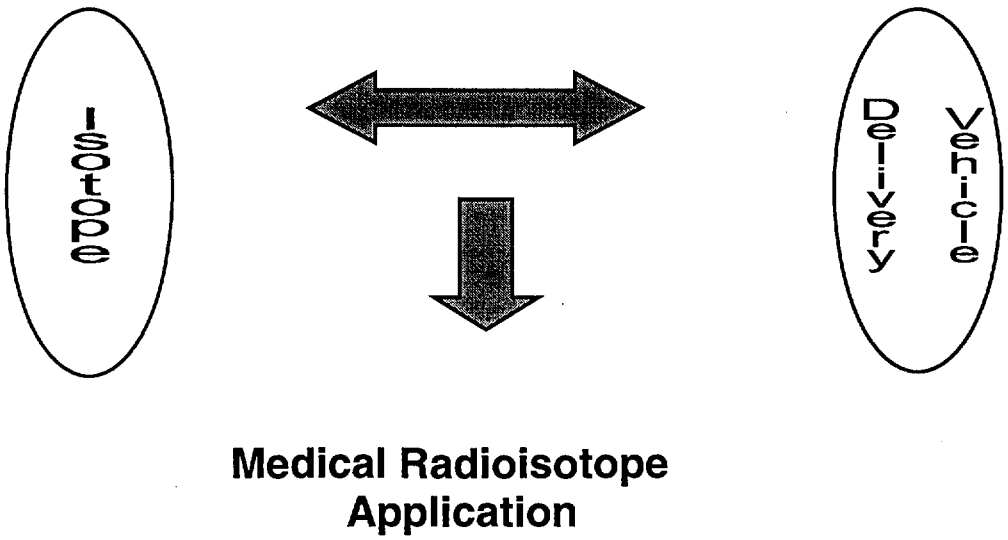
1. INTRODUCTION

The application of radioisotopes in medicine (called Nuclear Medicine) was first established over 30 years ago. In the early years of its application, Nuclear Medicine was an effective adjunct to the management of patient care. However, in recent years, with the development of newer agents and the dramatic improvement in gamma camera technology, medical radioisotopes have become an indispensable and growing component of the nation's health care system.

One important application of Nuclear Medicine makes a major contribution to the field of diagnostic imaging. Diagnostic Nuclear Medicine, X-ray, Computed Tomography (CT), ultrasound and Magnetic Resonance Imaging (MRI), all image internal body structures in a non-invasive way. CT scans use X-rays to build images of soft and hard tissues within the body, and MRI applies a nuclear magnetic resonance to image soft tissue. The images provided by CT and MRI are primarily of tissue structure with very little direct information provided on tissue function. In contrast to these techniques, diagnostic Nuclear Medicine provides functional information which enables not only visualization of structure but also information on how the structure is behaving and changing in real time.

This paper will deal with the main approaches to the use of radioisotopes for Nuclear Medicine and the future prospects for the area.

Figure 1. Schematic of the essential features of a clinical radiopharmaceutical.



2. DEVELOPMENT OF NEW RADIOPHARMACEUTICALS

Radioisotopes combined with a "delivery vehicle" (Figure 1) present increasing opportunities to improve patient care. The requirements for an effective medical radiopharmaceutical are:

- selectivity for disease state/organ of concern
- specificity
- optimum time to localisation
- low toxicity
- time of clearance from body
- physical and chemical properties of the radioisotope.

Each of these criteria needs to be satisfied for an effective radioisotope medical application. These factors will, of course, vary with the proposed application.

Table 1 gives an indication of how the properties of the radioisotope, for example half-life and range, can vary for different radioisotopes. This gives significant flexibility in selecting the properties of the clinical products.

Likewise, the "delivery vehicle" needs to be chosen to enable effective localisation of the chosen radioisotope. Examples of the range of current and potential delivery vehicles include:

- small molecule ligands
- peptides
- antibodies / fragments
- particulate solids

The choice is a function again of the designed outcomes.

There are a number of radiopharmaceuticals under development as new diagnostic and therapeutic agents. At present, there are over 100 new radioisotope procedures under preclinical and clinical evaluation. These cover a wide range of applications and are mainly directed at new applications of the radioisotope moiety.

3. DEMAND FOR RADIOISOTOPES

Over the past several years there have been four major reports on the projected future requirements for radioisotopes for medical application. These reports focus on the North American market (Table 2), and all predict a substantial increase in the application of radioisotopes over the next 20 years. An expert panel composed of physicians, government and industrial representatives recently reviewed these projections[1] and concluded that the expected growth rate of medical radioisotope usage during the next 20 years will be between 7-16% per annum for diagnostic applications, and 7 - 14% for therapeutic applications. The panel also reported the need to support the development of radioisotopes that have not yet been commercialised.

While these figures address the North American situation historically, the growth of radiopharmaceutical applications in Australia has mirrored that of North America since clinical requirements are similar in most developed countries.

Table 1. Physical characteristics of radioisotopes used for therapy arranged in order of maximum range

Nuclide	Half life	Emission	Maximum range
^{80m}Br	4.42 h	Auger	< 10 nm
^{125}I	60.0 d	Auger	10nm
^{211}At	7.2 h	alpha	65 μm
^{169}Er	9.5 d	beta	1 mm
^{67}Cu	2.58 d	beta/gamma	2.2 mm
^{131}I	8.04 d	beta/gamma	2.4 mm
^{153}Sm	1.95 d	beta/gamma	3.0 mm
^{198}Au	2.7 d	beta/gamma	4.4 mm
^{186}Re	3.77 d	beta/gamma	5.0 mm
^{165}Dy	2.33 h	beta/gamma	6.4 mm
^{89}Sr	50.5 d	beta	8.0 mm
^{32}P	14.3 d	beta	8.7 mm
^{90}Y	2.67 d	beta	12 mm

While there are no reports of the application of radioisotopes for specific medical conditions, there are general trends of use. The general trend over the last few years has been an increase in the number of patient doses. The main difference is the usage rate; in the USA it is approximately 40 procedures per 1000 population compared to just over 20 in Australia[2].

respectively. More recently I-123 labelled compounds have found application in thyroid and oncology imaging.

The second type of imaging modality is Positron Emission Tomography (PET). PET is a more recently developed technique and is reliant on short lived positron-emitting radioisotopes. With the PET camera, imaging depends on the simultaneous

Table 2. List of recent reports on the use of radioisotopes in medical applications.

Beneficial Uses and Production of Isotopes. AEN/NEA Report, 22 May 1998
Medical Isotopes Market Study (2001- 2020). Frost & Sullivan, 20 November 1997
Evaluation of Medical Radionuclide Production with the Accelerator Production of Tritium (APT) Facility Medical University of South Carolina, University of South Carolina and Westinghouse Savannah River ompany, 15 July 1997
Worldwide Isotope Market Update. Arthur Andersen & Co. SC, November 1994

4. TYPICAL APPLICATIONS OF RADIOPHARMACEUTICALS

Radioisotopes find application in three medical areas, namely for diagnosis, palliation or therapy.

In diagnostic Nuclear Medicine, a small amount of a radiolabelled compound is either injected, swallowed or inhaled. This compound becomes localised in the region of interest and radioactive decay is imaged using a suitable device (camera). There are basically two types of imaging modality. In the first type, conventional photon imaging systems and Single Photon Emission Tomography (SPECT) imaging techniques utilise gamma emitting radioisotopes. The most commonly used radioisotope is Tc-99m which is used in more than 60% of all diagnostic Nuclear Medicine procedures. Tc-99m based radiopharmaceuticals find application in the imaging of most forms of tissue since it is readily available to most, if not all, nuclear medicine practices. Tc-99m is readily produced from a "generator" which uses Mo-99 as a precursor, and the Tc-99m can be drawn off as required. Tc-99m is typically compounded with one of a number of biologically active substances to ensure that it specifically localises to the region of interest in the body. In this way Tc-99m is a very versatile agent and is called the "workhorse" of modern Nuclear Medicine. Because of the clinical convenience outlined above, where possible diagnostic agents are labelled with Tc-99m. Other radioisotopes in routine clinical use are Tl-201 and Ga-67 for cardiac and soft tissues imaging

detection of two gamma rays produced when a positron annihilation occurs. PET cameras are only just coming into general use and although there are only a few PET cameras in Australia, substantial growth is expected over the next few years. The most common PET radioisotope is F-18 produced by a cyclotron. The radiopharmaceutical widely used is fluro-18 deoxyglucose (FDG) produced in a complex process from F-18 (half-life 109 minutes). FDG is particularly useful in imaging areas of higher than normal metabolic activity and is therefore very effective in the detection and staging of cancers.

In addition to diagnostic Nuclear Medicine, palliation of pain associated with bone secondary metastases is a very important application of radioisotopes. Several studies have established the benefit of radiation in relieving the dramatic pain associated with this disease state. Bone seeking radioisotopes such as Sr-89 and Sm-153 are approved for this application[3]. Other agents based on Sn-117 and Re-188 are under development. Benefits to the patient include a reduction in the use of opiate analgesics and improved quality of life.

The most well established application in therapeutic Nuclear Medicine is the use of I-131 to treat thyroid cancer. This has been successfully applied for over 30 years with excellent remission rates. The success of this treatment is largely due to the high selective localisation of I-131 in the thyroid.

5. RECENT DEVELOPMENTS IN CLINICAL RADIOPHARMACEUTICALS

Table 3 is a list of recently approved radiopharmaceuticals for medical application.

Table 3. Recently approved medical radioisotopes.

Product	Isotope		Approval Body
CEA Scan	Tc-99m	colorectal cancer	FDA
Leukoscan	Tc-99m	Infection imaging	EU
Prostascint	In-111	prostrate cancer	FDA
Octreoscan	In-111	oncology - brain, breast	FDA/EU
Acutect	Tc-99m	thrombosis	FDA
CEAcide	Y-90	ovarian cancer therapy	FDA

Interestingly these products are mainly radiolabelled antibodies and peptide. CEA scan and Leukoscan are Tc-99m based monocolonal antibody products for selective imaging of colorectal cancer and infection, respectively. Prostacint, also an antibody, is labelled with In-111 and is used for imaging of prostate cancer. The peptide based agents, octreoscan (In-111) and acutect (Tc-99m), are applied to the imaging of brain/breast cancers and thrombosis, respectively.

Very recently, CEA-cide, the therapeutic analogue of CEA-Scan, was approved for clinical use in the treatment of breast cancer.

Research is very active in the development of therapeutic radioisotopes and there are a large number in preclinical and clinical investigation. The applications are diverse but mainly focus on cancer.

6. THE FUTURE

Medical radioisotopes have entered the mainstream of clinical practice because of their application and their special characteristics. With the Replacement Research Reactor and other developments at ANSTO Australia is well placed to take full advantage of these developments to provide the latest agents to improve quality of life.

REFERENCES

1. Forecast Future Demand for Medical Isotopes, March 1999, http://www.ne.doe.gov.
2. 1997/1998 Nuclear Medicine Census. Summary Report Analysis. TMG. September 1998.
3. Radioisotopes in the Treatment of Bone Metastases. Annals of Medicine, **29** (1997) 31-35.