Radioisotopes in Medicine

Nuclear Issues Briefing Paper 26

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- **Nuclear medicine uses radiation to provide diagnostic information about the functioning of a person's specific organs, or to treat them. Diagnostic procedures are now routine..**
- **Radiotherapy can be used to treat some medical conditions, especially cancer, using radiation to weaken or destroy particular targeted cells.**
- **Millions of nuclear medicine procedures are performed each year, and demand for radioisotopes is increasing rapidly.**

NUCLEAR MEDICINE

This is a branch of medicine that uses radiation to provide information about the functioning of a person's specific organs or to treat disease. In most cases, the information is used by physicians to make a quick, accurate diagnosis of the patient's illness. The thyroid, bones, heart, liver and many other organs can be easily imaged, and disorders in their function revealed. In some cases radiation can be used to treat diseased organs, or tumours.

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 one tenth of this.

Nuclear medicine was developed in the 1950s by physicians with an endocrine emphasis, initially using iodine-131 to diagnose and then treat thyroid disease. In recent years specialists have also come from radiology, as dual CT/PET procedures have become established.

DIAGNOSIS

Diagnostic techniques in nuclear medicine use radioactive tracers which emit gamma rays from within the body. These tracers are generally short-lived isotopes linked to chemical compounds which permit specific physiological processes to be scrutinised. They can be given by injection, inhalation or orally. The first type are where single photons are detected by a gamma camera which can view organs from many different angles. The camera builds up an image from the points from which radiation is emitted; this image is enhanced by a computer and viewed by a physician on a monitor for indications of abnormal conditions.

A more recent development is **Positron Emission Tomography** (PET) which is a more precise and sophisticated technique using isotopes produced in a cyclotron. A positron-emitting radionuclide is introduced, usually by injection, and accumulates in the target tissue. As it decays it emits a positron, which promptly combines with a nearby electron resulting in the simultaneous emission of two identifiable gamma rays in opposite directions. These are detected by a PET camera and give very precise indication of their origin. PET's most important clinical role is in oncology, with fluorine-18 as the tracer, since it has proven to be the most accurate non-invasive method of detecting and evaluating most cancers. It is also well used in cardiac and brain imaging.

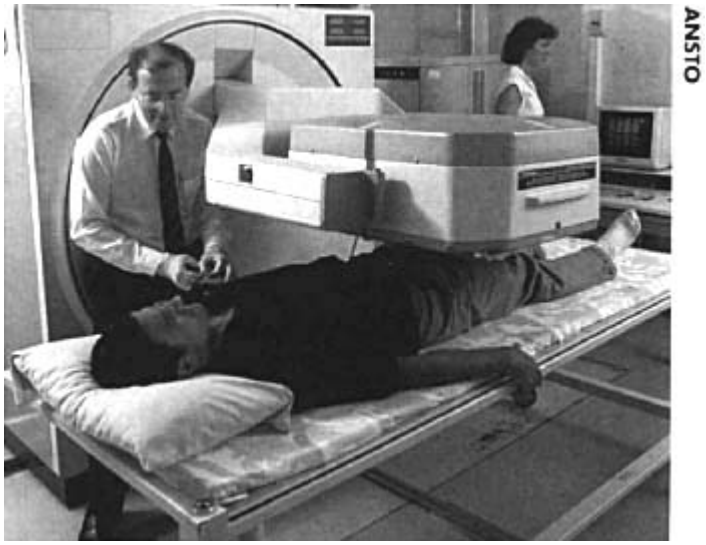
New procedures combine PET with CT scans to give co-registration of the two images, enabling 30% better diagnosis than with traditional gamma camera alone.

Positioning of the radiation source within the body makes the fundamental difference between nuclear medicine

imaging and other imaging techniques such as x-rays. Gamma imaging by either method described provides a view of the position and concentration of the radioisotope within the body. Organ malfunction can be indicated if the isotope is either partially taken up in the organ (cold spot), or taken up in excess (hot spot). If a series of images is taken over a period of time, an unusual pattern or rate of isotope movement could indicate malfunction in the organ.

A distinct advantage of nuclear imaging over x-ray techniques is that both bone and soft tissue can be imaged very successfully. This has led to its common use in developed countries where the probability of anyone having such a test is about one in two and rising.

The mean effective dose is 4.6 mSv per diagnostic procedure.



RADIOTHERAPY

Rapidly dividing cells are particularly sensitive to damage by radiation. For this reason, some cancerous growths can be controlled or eliminated by irradiating the area containing the growth. External irradiation can be carried out using a gamma beam from a radioactive cobalt-60 source, though in developed countries the much more versatile linear accelerators are now being utilised as a high-energy x-ray source (gamma and x-rays are much the same).

Internal radiotherapy is by administering or planting a small radiation source, usually a gamma or beta emitter, in the target area. Iodine-131 is commonly used to treat thyroid cancer, probably the most successful kind of cancer treatment. It is also used to treat non-malignant thyroid disorders. Iridium-192 implants are used especially in the head and breast. They are produced in wire form and are introduced through a catheter to the target area. After administering the correct dose, the implant wire is removed to shielded storage. This brachytherapy (short-range) procedure gives less overall radiation to the body, is more localised to the target tumour and is cost effective.

Treating leukaemia may involve a bone marrow transplant, in which case the defective bone marrow will first be killed off with a massive (and otherwise lethal) dose of radiation before being replaced with healthy bone marrow from a donor.

Many therapeutic procedures are palliative, usually to relieve pain. For instance, strontium-89 and (increasingly) samarium 153 are used for the relief of cancer-induced bone pain. Rhenium-186 is a newer product for this.

A new field is **Targeted Alpha Therapy (TAT)**, especially for the control of dispersed cancers. The short range of very energetic alpha emissions in tissue means that a large fraction of that radiative energy goes into the targeted cancer cells, once a carrier has taken the alpha-emitting radionuclide to exactly the right place.

Laboratory studies are encouraging and clinical trials for leukaemia, cystic glioma and melanoma are under way.

An experimental development of this is **Boron Neutron Capture Therapy** using boron-10 which concentrates in malignant brain tumours. The patient is then irradiated with thermal neutrons which are strongly absorbed by the boron, producing high-energy alpha particles which kill the cancer. This requires the patient to be brought to a nuclear reactor, rather than the radioisotopes being taken to the patient.

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.

BIOCHEMICAL ANALYSIS

It is very easy to detect the presence or absence of some radioactive materials even when they exist in very low concentrations. Radioisotopes can therefore be used to label molecules of biological samples in vitro (out of the body). Pathologists have devised hundreds of tests to determine the constituents of blood, serum, urine, hormones, antigens and many drugs by means of associated radioisotopes. These procedures are known as radioimmuno assays and, although the biochemistry is complex, kits manufactured for laboratory use are very easy to use and give accurate results.

DIAGNOSTIC RADIOPHARMACEUTICALS

Every organ in our bodies acts differently from a chemical point of view. Doctors and chemists have identified a number of chemicals which are absorbed by specific organs. The thyroid, for example, takes up iodine, the brain consumes quantities of glucose, and so on. With this knowledge, radiopharmacists are able to attach various radioisotopes to biologically active substances. Once a radioactive form of one of these substances enters the body, it is incorporated into the normal biological processes and excreted in the usual ways.

Diagnostic radiopharmaceuticals can be used to examine blood flow to the brain, functioning of the liver, lungs, heart or kidneys, to assess bone growth, and to confirm other diagnostic procedures. Another important use is to predict the effects of surgery and assess changes since treatment.

The amount of the radiopharmaceutical given to a patient is just sufficient to obtain the required information before its decay. The radiation dose received is medically insignificant. The patient experiences no discomfort during the test and after a short time there is no trace that the test was ever done. The non-invasive nature of this technology, together with the ability to observe an organ functioning from outside the body, makes this technique a powerful diagnostic tool.

A radioisotope used for diagnosis 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 radioisotope most widely used in medicine is **technetium-99m**, employed in some 80% of all nuclear medicine procedures. It is an isotope of the artificially-produced element technetium and it has almost ideal characteristics for a nuclear medicine scan. These are:

- It has a half-life of six hours which is long enough to examine metabolic processes yet short enough to minimise the radiation dose to the patient.
- Technetium-99m decays by a process called "isomeric"; which emits gamma rays and low energy electrons. Since there is no high energy beta emission the radiation dose to the patient is low.
- The low energy gamma rays it emits easily escape the human body and are accurately detected by a gamma camera. Once again the radiation dose to the patient is minimised.
- The chemistry of technetium is so versatile it can form tracers by being incorporated into a range of biologically-active substances to ensure that it concentrates in the tissue or organ of interest.

Its logistics also favour its use. Technetium generators, a lead pot enclosing a glass tube containing the

radioisotope, are supplied to hospitals from the nuclear reactor where the isotopes are made. They contain molybdenum-99, with a half-life of 66 hours, which progressively decays to technetium-99. The Tc-99 is washed out of the lead pot by saline solution when it is required. After two weeks or less the generator is returned for recharging.

A similar generator system is used to produce rubidium-82 for PET imaging from strontium-82 - which has a half-life of 25 days.

Myocardial Perfusion Imaging (MPI) uses thallium-201 chloride or technetium-99m and is important for detection and prognosis of coronary artery disease.

For PET imaging, the main radiopharmaceutical is Fluoro-deoxy glucose (FDG) incorporating F-18 - with a half-life of just under two hours, as a tracer. The FDG is readily incorporated into the cell without being broken down, and is a good indicator of cell metabolism.

In diagnostic medicine, there is a strong trend to using more cyclotron-produced isotopes such as F-18 as PET and CT/PET become more widely available. However, the procedure needs to be undertaken within two hours of a cyclotron.

THERAPEUTIC RADIOPHARMACEUTICALS

For some medical conditions, it is useful to destroy or weaken malfunctioning cells using radiation. The radioisotope that generates the radiation can be localised in the required organ in the same way it is used for diagnosis - through a radioactive element following its usual biological path, or through the element being attached to a suitable biological compound. In most cases, it is beta radiation which causes the destruction of the damaged cells. This is radiotherapy. Short-range radiotherapy is known as brachytherapy.

Although radiotherapy is less common than diagnostic use of radioactive material in medicine, it is nevertheless widespread, important and growing. An ideal therapeutic radioisotope is a strong beta emitter with just enough gamma to enable imaging, eg **lutetium-177**. This is prepared from ytterbium-176 which is irradiated to become Yb-177 which decays rapidly to Lu-177.

Iodine-131 and phosphorus-32 are examples of two radioisotopes used for therapy. Iodine-131 is used to treat the thyroid for cancers and other abnormal conditions such as hyperthyroidism (over-active thyroid). In a disease called Polycythemia vera, an excess of red blood cells is produced in the bone marrow. Phosphorus-32 is used to control this excess.

A new and still experimental procedure uses boron-10 which concentrates in the tumor. The patient is then irradiated with neutrons which are strongly absorbed by the boron, to produce high-energy alpha particles which kill the cancer.

For targeted alpha therapy (TAT), actinium-225 is readily available now, from which the daughter Bi-213 can be obtained (via 3 alpha decays) to label targeting molecules.

Considerable medical research is being conducted worldwide into the use of radionuclides attached to highly specific biological chemicals such as immunoglobulin molecules (monoclonal antibodies). The eventual tagging of these cells with a therapeutic dose of radiation may lead to the regression - or even cure - of some diseases.

ISOTOPES USED IN MEDICINE

Reactor Radioisotopes (half-life indicated)

Molybdenum-99 (66 h): Used as the 'parent' in a generator to produce technetium-99m.

Technetium-99m (6 h): Used in to image the skeleton and heart muscle in particular, but also for brain, thyroid,

lungs (perfusion and ventilation), liver, spleen, kidney (structure and filtration rate), gall bladder, bone marrow, salivary and lacrimal glands, heart blood pool, infection and numerous specialised medical studies.

Bismuth-213 (46 min): Used for TAT.

Chromium-51 (28 d): Used to label red blood cells and quantify gastro-intestinal protein loss.

Cobalt-60 (10.5 mth): Formerly used for external beam radiotherapy.

Copper-64 (13 h): Used to study genetic diseases affecting copper metabolism, such as Wilson's and Menke's diseases.

Dysprosium-165 (2 h): Used as an aggregated hydroxide for synovectomy treatment of arthritis.

Erbium-169 (9.4 d): Use for relieving arthritis pain in synovial joints.

Holmium-166 (26 h): Being developed for diagnosis and treatment of liver tumours.

Iodine-125 (60 d): Used in cancer brachytherapy (prostate and brain), also diagnostically to evaluate the filtration rate of kidneys and to diagnose deep vein thrombosis in the leg. It is also widely used in radioimmuno-assays to show the presence of hormones in tiny quantities.

Iodine-131 (8 d): Widely used in treating thyroid cancer and in imaging the thyroid; also in diagnosis of abnormal liver function, renal (kidney) blood flow and urinary tract obstruction. A strong gamma emitter, but used for beta therapy.

Iridium-192 (74 d): Supplied in wire form for use as an internal radiotherapy source for cancer treatment (used then removed).

Iron-59 (46 d): Used in studies of iron metabolism in the spleen.

Lutetium-177 (6.7 d): Lu-177 is increasingly important as it emits just enough gamma for imaging while the beta radiation does the therapy on small (eg endocrine) tumours. Its half-life is long enough to allow sophisticated preparation for use.

Palladium-103 (17 d): Used to make brachytherapy permanent implant seeds for early stage prostate cancer.

Phosphorus-32 (14 d): Used in the treatment of polycythemia vera (excess red blood cells). Beta emitter.

Potassium-42 (12 h): Used for the determination of exchangeable potassium in coronary blood flow.

Rhenium-186 (3.8 d): Used for pain relief in bone cancer. Beta emitter with weak gamma for imaging.

Rhenium-188 (17 h): Used to beta irradiate coronary arteries from an angioplasty balloon.

Samarium-153 (47 h): Sm-153 is very effective in relieving the pain of secondary cancers lodged in the bone, sold as Quadramet. Also very effective for prostate and breast cancer. Beta emitter.

Selenium-75 (120 d): Used in the form of seleno-methionine to study the production of digestive enzymes.

Sodium-24 (15 h): For studies of electrolytes within the body.

Strontium-89 (50 d): Very effective in reducing the pain of prostate and bone cancer. Beta emitter.

Xenon-133 (5 d): Used for pulmonary (lung) ventilation studies.

Ytterbium-169 (32 d): Used for cerebrospinal fluid studies in the brain.

Ytterbium-177 (1.9 h): Progenitor of Lu-177.

Yttrium-90 (64 h): Used for cancer brachytherapy and as silicate colloid for the relieving the pain of arthritis in larger synovial joints. Pure beta emitter.

Radioisotopes of caesium, gold and ruthenium are also used in brachytherapy.

Cyclotron Radioisotopes

Carbon-11, Nitrogen-13, Oxygen-15, Fluorine-18:
These are positron emitters used in PET for studying brain physiology and pathology, in particular for localising epileptic focus, and in dementia, psychiatry and neuropharmacology studies. They also have a significant role in cardiology. F-18 in FDG has become very important in detection of cancers and the monitoring of progress in their treatment, using PET.

Cobalt-57 (272 d): Used as a marker to estimate organ size and for in-vitro diagnostic kits.

Gallium-67 (78 h): Used for tumour imaging and localisation of inflammatory lesions (infections).

Indium-111 (2.8 d): Used for specialist diagnostic studies, eg brain studies, infection and colon transit studies.

Iodine-123 (13 h): Increasingly used for diagnosis of thyroid function, it is a gamma emitter without the beta radiation of I-131.

Krypton-81m (13 sec) from Rubidium-81 (4.6 h): Kr-81m gas can yield functional images of pulmonary ventilation, e.g. in asthmatic patients, and for the early diagnosis of lung diseases and function.

Rubidium-82 (65 h): Convenient PET agent in myocardial perfusion imaging.

Strontium-92 (25 d): Used as the 'parent' in a generator to produce Rb-82.

Thallium-201 (73 h): Used for diagnosis of coronary artery disease other heart conditions such as heart muscle death and for location of low-grade lymphomas.

What are radioisotopes?

Many of the chemical elements have a number of isotopes. The isotopes of an element have the same number of protons in their atoms (atomic number) but different masses due to different numbers of neutrons. In an atom in the neutral state, the number of external electrons also equals the atomic number. These electrons determine the chemistry of the atom. The atomic mass is the sum of the protons and neutrons. There are 82 stable elements and about 275 stable isotopes of these elements.

When a combination of neutrons and protons, which does not already exist in nature, is produced artificially, the atom will be unstable and is called a radioactive isotope or radioisotope. There are also a number of unstable natural isotopes arising from the decay of primordial uranium and thorium. Overall there are some 1800 radioisotopes.

At present there are up to 200 radioisotopes used on a regular basis, and most must be produced artificially.

Radioisotopes can be manufactured in several ways. The most common is by neutron activation in a nuclear reactor. This involves the capture of a neutron by the nucleus of an atom resulting in an excess of neutrons

(neutron rich). Some radioisotopes are manufactured in a cyclotron in which protons are introduced to the nucleus resulting in a deficiency of neutrons (proton rich).

The nucleus of a radioisotope usually becomes stable by emitting an alpha and/or beta particle (or positron). These particles may be accompanied by the emission of energy in the form of electromagnetic radiation known as gamma rays. This process is known as radioactive decay.

Radioactive products which are used in medicine are referred to as radiopharmaceuticals.

Appendix to Nuclear Issues Briefing Paper 26

New reactor needed for medical imaging - why cyclotrons cannot do the job

Article from May 1999 edition Australasian Science Magazine

June 1999

Rex Boyd defends the decision to commission a new nuclear reactor.

It is claimed by opponents of the nuclear industry that Australia's demand for medical radioisotopes can be met by cyclotrons. The truth is that any number of cyclotrons will never replace Australia's need for a reactor.

Australia has two cyclotrons, which use high voltages and electrical fields to accelerate hydrogen atoms through a vacuum chamber. When they collide with a target substance they produce radioactivity.

As a general rule, it is more difficult to make a radioisotope in a cyclotron than in a reactor. Cyclotron reactions are less productive and less predictable than nuclear reactions performed in a reactor.

The cyclotron produces neutron-deficient radioisotopes whereas the reactor produces neutron-rich radioisotopes. Thus the reactor and the cyclotron complement each other in satisfying society's need for a full range of radioisotopes; rarely one acts as a substitute for the other.

A few radioisotopes are exceptions to this rule and can be produced by either facility. One is technetium-99m, currently used in 85% of medical applications. The discovery that technetium-99m can be produced in a cyclotron does not imply that the need for a reactor is disappearing.

The half-life of technetium-99m is 6 hours. This means that this radioisotope must be produced and distributed on a daily basis.

However, when technetium-99m is produced in a reactor it proceeds through a precursor radioisotope, molybdenum-99, which has a half-life of 66 hours. Thus the weekly production of molybdenum-99 generators can meet all the technetium-99m needs of Australian hospitals.

In contrast the cyclotron does not produce molybdenum-99; instead it produces technetium-99m directly. Therefore a network of cyclotrons situated across Australia would be needed to make daily deliveries of technetium-99m to the nation's hospitals. This is one reason why none of the many powerful cyclotrons around the world are used for the manufacture of technetium-99m.

Reliance on cyclotrons for our most frequently used medical isotope would have a serious negative impact on the practice of nuclear medicine. The rapid decay of technetium-99m would limit the number of patients treated in any one day and would preclude the use of nuclear medicine techniques in out-of-hours emergency situations

when stocks would be exhausted. Appointments would be subject to technetium-99m availability and patient waiting lists would lengthen.

Economic factors would also militate against cyclotron-produced technetium-99m. The raw materials for reactor production are cheap (a few dollars per kilogram) and readily available, whereas the starting material for the cyclotron-method is a rare form of molybdenum that must be enriched to high levels of isotopic purity (>99%), is not commercially available and would cost millions of dollars per kilogram.

Traces of other molybdenum isotopes in the raw materials can reduce the purity of the technetium-99m. A series of competing nuclear reactions produces undesirable longer-lived technetium radioisotopes, particularly technetium-96, that can accumulate during the day. The level of these impurities may exceed the legal limit and degrade the quality of the scanned image.

Other technetium radioisotopes would expose patients to higher radiation doses. Only 0.1% technetium-96 is necessary before radiation exposure of patients is doubled. Hence before cyclotron-produced technetium-99m could be used, certain regulations governing radiopharmaceutical quality would need changing.

The cyclotron production of technetium-99m is technically feasible but undesirable for all of these reasons.

The frontiers of nuclear medicine now extend beyond the diagnosis of disease with technetium-99m. Other short-lived radioisotopes are being introduced into nuclear medicine with the capability of reducing the pain associated with cancer. Australia must have its own reactor if its community is to have access to these radioisotopes and reap the benefits of the latest advances.

Rex Boyd was formerly the director of the $20 million National Medical Cyclotron Project at Sydney's Royal Prince Alfred Hospital.

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ANSTO, and papers at 1999 and 2001 ANA conferences.
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