Cyclotron-Produced Radioisotopes and their Clinical Use at the Austin PET Centre

H.J. TOCHON-DANGUY, Senior Radiochemist, Centre For PET, Austin & Repatriation Medical Centre, Melbourne Victoria 3084

SUMMARY A Centre for Positron Emission Tomography (PET) has been established within the Department of Nuclear Medicine at the Austin & Repatriation Medical Centre (A&RMC) in Melbourne. PET is a non-invasive technique based on the use of biologically relevant compounds labelled with short-lived positron-emitting radionuclides such as carbon-11, nitrogen-13, oxygen-15 and fluorine-18. The basic equipment consists of a medical cyclotron (10 MeV proton & 5 MeV deuteron), six lead-shielded hotcells with associated radiochemistry facilities and a whole body PET scanner. During its first five years of operation, the Melbourne PET Centre, has pursued a strong radiolabelling development program, leading to an ambitious clinical program in neurology, oncology and cardiology.

1 INTRODUCTION

Positron emission tomography (PET) is an imaging technique that provides *in vivo* measurements in absolute units of a radioactive tracer. The PET technique offers the unique possibility of studying metabolic and physiological processes in living human subjects without disturbing the system under investigation (1). One of the attractive aspects of PET is that the radioactive tracer can be labelled with short-lived radioisotopes of the natural elements of the biochemical constituents of the body. For example, natural atoms of carbon, nitrogen and oxygen are replaced with the short-lived positron-emitting radioisotopes carbon-11 ($t_{½}$=20.4 min), nitrogen-13 ($t_{½}$=10 min) and oxygen-15 ($t_{½}$=2 min). In addition, fluorine-18 ($t_{½}$=109.6 min) can be exchanged for hydrogen in the molecule.

Twenty years ago the short-lived radionuclides were available only in the large centres for physical research owning particle accelerators or nuclear reactors. Today the increasing clinical applications of cyclotron produced radionuclides and radiopharmaceuticals rapidly raised the number of compact cyclotrons throughout the world. Up to 120 medical cyclotrons have been established worldwide in the past 15 years with two cyclotron facilities in operation in Australia: Melbourne (2) and Sydney (3). Medical cyclotrons may be classified into two groups, depending on the maximum energy of the beam available: i) cyclotrons with fixed energies of 10-17 MeV protons (5-8 MeV deuterons); ii) cyclotrons with variable energy up to 35 MeV protons (17 MeV deuterons). These medical cyclotrons are generally dual particle machines (proton & deuteron) to take advantage of a broad spectrum of nuclear reactions, and the main differences between the two groups being the number and quantities of radionuclides which can be produced. All medical cyclotrons that are currently available are suitable for sustaining a major program in positron emitter production for PET research and clinical application. It is the purpose of this article to briefly describe the Austin's PET facilities and to explore the initial 5 years of operation. We describe the basic principles of the PET technique and review the cyclotron-produced radioisotopes and radiopharmaceuticals. Radiolabelling development programs and clinical applications are also addressed.

2 BASIC PRINCIPLES OF PET

This non-invasive imaging technique is based on the use of biologically relevant compounds labelled with short-lived positron-emitting radionuclides. In clinical applications, a very small amount of labelled compound (called radiopharmaceutical or radiotracer) is introduced into the patient usually by intravenous injection and the concentration in tissue measured by the scanner. During its decay process, the radionuclide emits a positron which, after traveling a short distance, encounters an electron from the surrounding environment. The two particles combine and "annihilate" each other resulting in the emission in opposite directions of two gamma rays of 511 KeV each (Figure 1).

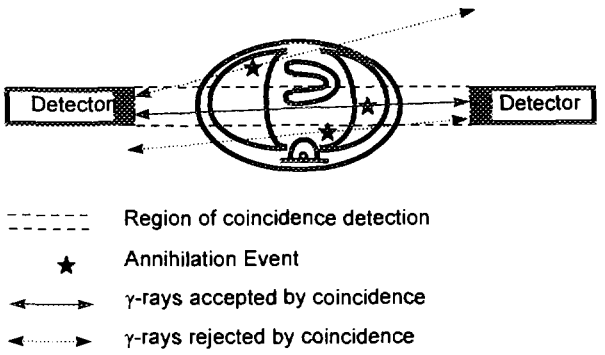

Figure 1. Basic principal of PET: coincidence detection

The image acquisition is based on the external detection in coincidence of the γ -rays and therefore the localisation of the positron-emitting radionuclides inside the patient. A tissue attenuation correction is performed by recording a short transmission scan using three Germanium-68 rotating rod sources. All the data are fed into a fast computer that reconstructs the images using a two dimensional or three-dimensional algorithm. Ultimately using various bio-mathematical models, these data will be transformed into information with physiological, pathological or pharmacological significance.

The main applications of PET to date, have been for studies of the human brain (4) and heart (5). More recently applications in oncology have shown very promising results (6). Several hundred radiopharmaceuticals have been labelled with positron emitters during the past two decades, and about 30 are presently considered to be of major interest in clinical PET (7).

A standard commercial PET scanner such as the Siemens/CTI 951 installed at the Austin Hospital in Melbourne comprises of 16 rings of bismuth germanate (BGO) detectors, covering an axial length of 10.8 cm with a ring aperture of 56.7 cm in diameter.

3 CYCLOTRON & TARGETERY SYSTEM

Cyclotron

The cyclotron in operation at the Austin & Repartriation Medical Centre in Melbourne is a negative ion design (Cyclone 10/5 from ION BEAM APPLICATIONS, Belgium) which accelerates H^- ion to 10 MeV and D^- ion to 5 MeV. At the extraction radius, the negative particles are stripped of their electrons by passing through a very thin stripping carbon foil and the resulting positively charged ions (H^+ & D^+) are bent outwards to the target ports, by the magnetic field. The design of the machine utilises a deep-valley magnetic field concept such that both the ion sources and radiofrequency accelerating cavities are located in two opposite valleys between the magnetic pole pieces. This allows the poles to be positioned much closer together and therefore considerably reduces the power consumption of the cyclotron. With the new sources, recently upgraded by the manufacturer on our machine, up to 80 μA of proton and 30 μA of deuteron beam intensity can be extracted onto a single target or divided between two oppositely mounted targets. The cylindrical magnet return yoke consisting of 15 cm of steel acts as the primary radiation shield and in addition the machine is enclosed inside a cylindrical shielding system consisting of 68 cm thickness of boron doped water. Experimental measurements indicate that the cyclotron shielding, together with the 60 cm thick concrete wall of the wault, is sufficient to keep the radiation dose level outside the cyclotron vault to less than 0.5 μSv/h.

Targetery

The Cyclon 10/5 can be fitted with 8 targets mounted directly on the vacuum chamber perimeter located inside the return yoke of the magnetic field. Two types of target are available from the manufacturer: a liquid target accepting various volume chamber inserts (aluminium or silver) ranging from 300μL to 1500μL; and a gas target (aluminium) with a fixed volume of 20 mL. Currently our machine is fitted with 6 targets remotely loaded or unloaded by gas pressures, and the radioisotopes are automatically transported via narrow tubing from the targets to the chemistry units in the hotcells laboratory. Two types of lead shielded hotcells have been installed within the laboratory: two large hotcells mainly used for R & D; and four small shielded cells used to house automated radiochemistry modules for routine radiopharmaceutical production.

4 PRODUCTION OF RADIOISOTOPES & RADIOPHARMACEUTICALS

Radioisotope production

The energy of the particle and the current of the particle beam as well as the cross section of the nuclear reaction itself, determine the quantity of radionuclide that can be produced in any time period. Experiments have shown that appropriate amounts of the four positron emitters commonly used in PET (^{15}O, ^{13}N, ^{11}C and ^{18}F) could be obtained with 10 MeV protons and 5 MeV deuterons. Table I lists our typical production yields and the nuclear reaction involved in the production of these four radionuclides.

radionuclides	nuclear reaction	production yield
Oxygen-15	$^{14}N(d,n)^{15}O$	300mCi (12MBq)
Nitrogen-13	$^{16}O(p,\alpha)^{13}N$	100mCi (4MBq)
Carbon-11	$^{14}N(p,\alpha)^{11}C$	800mCi (32MBq)
Fluorine-18	$^{18}O(p,n)^{18}F$	800mCi (32MBq)

Table 1. Typical production yields for the currently used positron emitters

Oxygen-15 and carbon-11 isotopes are both produced from a gas target. These targets can be run in either continuous flow or bolus mode at a loading pressure of up to 11 bar. The possibility of accelerating low energy deuterons offers the advantage of producing oxygen-15 from natural nitrogen gas, as target material, through the $^{14}N(d,n)^{15}O$ reaction. If restricted to a single particle cyclotron (proton), production of high specific activity oxygen-15 will require the use of the expensive nitrogen-15 isotope as a target material through the $^{15}N(p,n)^{15}O$ reaction. When high specific activity is not an issue, oxygen-15 can also be produced through the $^{16}O(p,pn)^{15}O$ reaction, ending with a $^{15}O/^{16}O$ oxygen mixture. Oxygen-15 can be produced as molecular oxygen ($^{15}O_2$), or directly as carbon dioxide ($C^{15}O_2$) by mixing the target gas with 5% of natural carbon dioxide as a carrier. Carbon monoxide ($C^{15}O$) can also be easily produced by reduction of $C^{15}O_2$ on activated charcoal at 900°C.

Carbon-11 is easily produced by proton bombardment of natural nitrogen-14 through the $^{14}N(p,\alpha)^{11}C$ nuclear reaction. A target gas mixture of a few percent oxygen in natural nitrogen will produce radioactive carbon dioxide ($^{11}CO_2$) and a few percent hydrogen in natural nitrogen will produce methane ($^{11}CH_4$). Carbon monoxide (^{11}CO) could also be easily produced by reduction of $^{11}CO_2$ on activated charcoal at 900°C.

To date, one of the most commonly used methods for ^{11}C-radiolabelling of PET radiotracers is through ^{11}C-methylation using ^{11}C-methyl iodide ($^{11}CH_3I$). The current method of production of $^{11}CH_3I$ is through the reduction of $^{11}CO_2$ using $LiAlH_4$, followed by aqueous HI reaction. This method suffers from the major disadvantage of natural carbon dioxide ($^{12}CO_2$) contamination, resulting in a much lower specific activity of $^{11}CH_3I$ than the original $^{11}CO_2$. The theoretical specific activity of $^{11}CO_2$ produced could be as high as 10 Ci/pmol but could drop below 5 Ci/μmol after radiolabelling of the $^{11}CH_3I$ precursor (9). To overcome this problem, an alternative gas phase production of $^{11}CH_3I$ from $^{11}CH_4$ has been recently investigated (10).

Nitrogen-13 and fluorine-18 isotopes are both produced from a liquid target. Nitrogen-13 is produced by proton bombardment of distilled water through the $^{16}O(p,\alpha)^{13}N$ nuclear reaction. Even with the relatively low energy proton beam delivered by our cyclotron (10 MeV) a useful production yield of 100 mCi can be achieved with 20 minutes irradiation. Up to recently, Nitrogen-13 was recovered mainly as nitrogen oxides ($^{13}NO_x$) in aqueous solution and a Devarda alloy was necessary to reduce the nitrite and nitrate into the more useful chemical form ammonia ($^{13}NH_3$). Today, the use of a scavenger for oxidising radicals, such as ethanol (5 mM), has been successfully used as to prevent in-target oxidation (11).

Fluorine-18 is produced by proton bombardment of oxygen-18 enriched water through the $^{18}O(p,n)^{18}F$ nuclear reaction. Fluorine-18 is recovered as an aqueous solution of fluoride-18 ($H_2O/^{18}F^-$), and can be easily extracted by ion exchange. Ionic fluoride-18 can be transfered into an organic solvent and used for stereospecific nucleophilic substitutions. Routinely 800 mCi of fluorine-18 can be produced in one hour of irradiation. It is important to mention that fluorine-18 can also be produced as a radioactive gas through the $^{20}Ne(d,\alpha)^{18}F$ nuclear reaction. This way of production, which is useful for electrophilic substitution, requires the addition into the target of fluorine-19 gas as carrier, and is currently seen as a less attractive method.

Radiopharmaceutical productions

The synthesis of radiolabelled compounds is one of the most critical aspects of the sequence of events in PET studies. In theory, with ^{11}C, any organic molecule could be labelled by isotopic substitution of ^{11}C for natural carbon, retaining the full properties of the parent molecule. In reality the short half-life of the positron emitting radioisotope imposes some constraints on labelling strategies. Thus access to ^{11}C as well as ^{13}N, ^{15}O and ^{18}F is essential in a flexible program of radiopharmaceutical design. Radiolabelling of compounds involves considerable amounts of radioactivity to start with and must be performed by remote control in lead-shielded hotcells. Time is an important factor in radiolabelling and new synthetic procedures are usually required to introduce the radioisotope in the latest possible stage of the synthesis. The final obligation is the biochemical evaluation of the radiopharmaceutical in terms of quality assurance and quality control (12). This includes chemical and radiochemical purity determination as well as pharmaceutical validation. In addition, when

receptor site mapping and quantitation are investigated, appropriate chemistry procedures must be carried out to ensure a high specific activity of the radiopharmaceutical, in the Ci/μmol (37 GBq/μmol) range. In Table 2 are listed the radiotracers and radiopharmaceuticals synthesised and used during the initial 5 years operation of our PET facility.

Radiotracers & radiopharmaceuticals	Examples of biomedical applications
^{15}O-oxygen	oxygen metabolism
^{15}O-carbon monoxide	blood volume
^{15}O-carbon dioxide	blood flow
^{15}O-water	blood flow
^{13}N-ammonia	blood flow
^{18}F-FDG	glucose metabolism
^{18}F-FMISO	hypoxic cell tracer
^{11}C-SCH23390	dopamine D1 marker
^{11}C-Flumazenil	benzodiazepine marker

Table 2. PET Radiotracers and radiopharmaceuticals produced at the Austin Centre and example of biomedical applications

As mentioned above, some PET radiotracers could be directly produced out of the target without further chemistry. This is the case for ^{15}O-labelled oxygen, carbon monoxide or carbon dioxide and for ^{13}N-labelled ammonia. Other radiotracers such as ^{15}O-labelled water could be synthesised on-line from the cyclotron-produced radioisotope itself, using a palladium-catalysed reaction (13). More complex molecules such as 2-Fluoro-2-Deoxy-D-Glucose (FDG), Fluoromisonidazole (FMISO) or Flumazenil (Ro 15-1788), radiolabelled with ^{18}F or ^{11}C, will require more sophisticated radiochemistry (14-16). A multi-step radiosynthesis is usually performed using an automated chemistry module and purification with High Pressure Liquid Chromatography (17).

5 PET CLINICAL APPLICATIONS

Clinical operation of the Austin PET Centre in Melbourne commenced in 1992 with 20 scans per month (18). After the initial few years of operation needed to develop and validate appropriate protocols and procedures, the patient throughput gradually increased to nearly 1000 scans per year in 1997. With now up to 9 radiotracers & radiopharmaceuticals routinely produced in the Centre, various relevant clinical parameters can be assessed including glucose metabolism, hypoxia, blood flow and neuroreceptor mapping.

Glucose metabolism

Since its development ^{18}FDG has become the most widely used radiopharmaceutical in the PET clinic today. ^{18}FDG uptake in biological tissue reflects glucose metabolism and could be used as a marker of cell dysfunction. To date, the clinical usage of ^{18}FDG at the Austin PET Centre has been concentrated in the following areas:

-to characterise various tumors and enable the effects of therapy to be monitored (19,20). A correlation has been found between the glucose accumulation by tumor and the degree of malignancy.

-to help in the selection of patients for surgical treatment of epilepsy (21). In three-quarters of patients with complex partial seizures, epileptogenic tissue has been identified as an area of hypometabolism.

-to identify patients likely to benefit from myocardial revascularization (22). Ischemic myocardium maintains its viability by increasing glycolytic flux rate, resulting in an ^{18}FDG tissue accumulation.

Hypoxic tissue visualisation

A nitroimidazole derivative, ^{18}F-Fluoromisonidazole (^{18}FMISO), is a relatively new tracer able to selectively identify hypoxic tissue by metabolic trapping in cells with reduced oxygen. To date, the initial clinical usage of ^{18}FMISO at the Austin PET Centre has been concentrated in two pilot studies:

-to gain an understanding of hypoxia within brain tumors (23). It has been suggested that reduced oxygen within tumors may be a factor in resistance to standard radiotherapy and chemotherapy.

-to identify tissues likely to represent the ischaemic penumbra in patients after acute ischaemic stroke (24). These findings may have important implications for the therapeutic window after stroke.

Oxygen metabolism and blood flow

The function of the cerebral tissue depends critically on the use of oxygen, and impairment in its rate of consumption often constitutes a pathological condition. The PET method represents a potentially valuable tool for the study of functional neuroanatomy in various pharmacological and diseased states. To date the initial usage of $^{15}O_2$, $C^{15}O_2$ and $H_2{}^{15}O$ at the Austin PET Centre has been concentrated on a few research protocols:

-to help in predicting outcomes and patient management after ischemic stroke (25). Using $^{15}O_2$ and $H_2{}^{15}O$ with PET, oxygen consumption and cerebral perfusion can be quantitatively measured in ischaemic stroke.

-to define areas of increased neural activity associated with specific motor or cognitive tasks in conscious man (26,27). The short half-life of oxygen-15 (2.1 min) allows for rapid sequential studies of cerebral blood flow using $H_2{}^{15}O$.

In addition, PET studies using radiotracers such as ^{13}N-ammonia allow for qualitative and quantitative regional coronary blood flow evaluation in coronary artery disease (28).

Receptor mapping

Several neurological and psychiatric diseases have been related to neurotransmitter and receptor disorders. There now exist PET radiotracers for mapping and quantifying many neuroreceptors including the dopamine receptor, the serotonin receptor, and the benzodiazepine receptor. Through PET studies, it is then possible to relate changes in neurotransmitter function to clinical features. To date, at the Austin PET Centre, only ^{11}C-Flumazenil has been used in the following clinical research:

-to evaluate the use of ^{11}C-Flumazenil for preoperative visualisation and localisation of epileptic foci in patients with intractable partial epilepsy (29). It has been demonstrated that the density of postsynaptic benzodiazepine receptors is reduced in human epileptic foci.

-to quantify the number and affinity of cerebral benzodiazepine receptors in the pathogenesis of various psychiatric disorders such as post traumatic stress disorder (PTSD) and panic disorder (30). There is widespread therapeutic use of benzodiazepines for their pharmacological actions such as anxiolitic, anticonvulsant and sedative-hypnotic effects. The actions of the benzodiazepines are thought to be caused by enhancing the effects of GABA-mediated inhibition in the central nervous system.

6 FUTURE DEVELOPMENTS

The preparation and the use of new labelled PET radiopharmaceuticals is fundamental for the development of further clinical studies. Two areas, oncology and psychiatry, offer particularly challenging field of development for PET.

In oncology, PET has already been found useful in assessing the viability of tumors and the efficacy of anti-cancer drugs. Although ^{18}FDG provides information on tumor metabolism, it has limited utility in certain tumors with lower grades of metabolism. In addition it has been shown that glucose metabolism changes occur much later than changes in nucleic acid metabolism. Thus nucleoside analogues represent a structural class regarded as potential marker of DNA proliferation, and thymidine derivatives are currently under evaluation at the Austin PET Centre.

In psychiatry, PET has already shown some useful applications in the understanding of the biochemical processes in cerebral function. Serotoninergic neuron abnormalities have been suggested in neuropsychiatric diseases, and extensive efforts have been made to radiolabel antidepressant drugs which bind to 5-HT sites on the serotoninergic neuron terminals. Most of these compounds have been found unsuitable for PET studies, and radiolabelling of a new highly potent serotonin uptake blocker is under investigation at the Austin PET Centre.

7 CONCLUSIONS

The interest in PET is now well established in medical research. The strength of PET lies in its ability to provide quantitative functional information about physiology *in vivo*. The examples of the use of PET to examine structure-function relationships, have proved to be useful in clinical domains such as oncology, cerebrovascular or myocardial disease and neuropathophysiology.

The proven ability of PET to image and quantify physiological and chemical processes provides clinicians with a unique means of guiding diagnosis and treatment. The role for PET will continue to be expanded as more chemically specific tracers are developed for probing normal and abnormal biological function. However, optimal application of PET to the measurement of regional tissue function is complicated and depends on a wide variety of expertise.

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