THE MEDICAL APPLICATIONS OF SHORT-LIVED, CYCLOTRON-PRODUCED RADIONUCLIDES[1]

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Recent reviews are available of the cyclotrons used in medical applications[1], and of the radiopharmaceuticals that are labeled with short-lived, cyclotron-produced radioisotopes[2]. This paper will therefore focus on current nuclear medicine trends and their potential impact on the designs of medical accelerator-based radiopharmaceutical production systems.

There are two classes of cyclotron-produced radioisotopes used in nuclear medicine today: (1) photon-emitting radionuclides that are used with the gamma camera; and (2) positron-emitting radionuclides that are used with the new positron tomographic scanners. The former have achieved widespread clinical application, while the latter group is being used in the development of an important new approach to the in vivo study of regional physiology.

Photon-Emitting Isotopes

Perhaps the most important new technique in nuclear medicine is rest-exercise ^{201}Tl myocardial imaging. Since the biologic behavior of ^{201}Tl was first described in 1975[3], a rapidly growing number of nuclear medicine departments have begun to use this radioisotope in the detection, localization and evaluation of areas of reduced blood flow in the myocardium. The protocol for such a study calls for the patient to strenuously exercise immediately prior to the injection of the radiopharmaceutical, [^{201}Tl] thallous chloride, in order to emphasize the region of reduced flow. The patient is then injected and scanned with a gamma camera that has high count rate capabilities and facilities for acquiring and displaying the data for each phase of the heart cycle separately. This technique is non-invasive and avoids the increasing concerns over the risks involved in the catheterization procedure used for x-ray analysis of the myocardium. In patients with symptoms suggesting coronary disease, a sensitivity of 75-95% and a specificity of 85-95% have been reported[4-7] for the detection of coronary disease when compared to coronary arteriography.

The reasons for the selection of ^{201}Tl include the following: (1) the thallous ion (Tl^+) is a good analog to the potassium ion (K^+) which is the main intercellular cation of the myocardium; (2) this isotope has good emission characteristics for imaging with the conventional gamma camera; (3) it can be obtained from a parent isotope, ^{201}Pb, which has a 9.4 h half-life; and (4) ^{201}Tl has a 73 h half-life which is convenient for shipment and storage for emergencies. These factors make ^{201}Tl more desirable for clinical applications than any of the isotopes of potassium, rubidium and cesium that have been evaluated [8-12].

The production requirements for ^{201}Tl are described in Ref. 13. From the excitation curves shown in this reference it can be seen that a proton beam energy of 25 MeV or greater is required to produce this isotope in large quantities at high specific activities.

Because of the increasing utilization of ^{201}Tl and other photon-emitting accelerator-produced isotopes, at least one commercial radiopharmaceutical supplier is considering developing a high current linear accelerator rather than continuing to build more cyclotrons [14]. With this level of commercial interest in these isotopes it is unlikely that individual hospitals will find it economical to acquire and operate compact medical cyclotrons to provide these isotopes. The future for hospital cyclotrons would seem to be more in the direction of providing only those isotopes that have too short a half-life to permit shipment and hence are not suitable for the economies of high volume commercial production.

Positron-Emitting Radioisotopes

With the development of the positron tomographic scanner (see Ref. 15 for a description of one such scanner, and Ref. 16 for a complete bibliography covering the development of this imaging technique), better use is being made of the advantages of ^{11}C, ^{13}N, ^{15}O and ^{18}F as labels for biochemicals and their analogs. Positron tomographic images can be used for the quantitative determination of the regional concentration of physiologically participative radiopharmaceuticals. From these measurements one can non-invasively determine the values of physiological rate "constants" within these small regions and thereby achieve a more detailed understanding of the physiological state.

An example of the application of positron tomography to the assessment of physiologic rate constants is the measure of regional cerebral glucose metabolism using ^{18}F-2-fluoro-2-deoxyglucose [17-21]. In this technique a multi-compartmental model was defined and first-order rate constants were assumed to describe the active transport of the labeled compounds between these compartments. Average values of these rate constants were determined via a constant infusion procedure, and these average values were shown to be useful for the determination of the regional glucose utilization rates from the counts in the positron tomographic image. The glucose utilization can be related to the oxygen consumption in these small regions since glucose is the sole metabolic substrate in the brain under most conditions [22,23]. Using this technique one is then able to study the energy utilization in small regions of gray or white matter in different functional areas of the brain. This capability can potentially be applied to the basic study of physiology, as in the mapping of the

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functional neural pathways of the brain, as well as in the diagnosis of cerebral disease or the assessment of the response to therapeutic intervention.

The primary isotopes used in positron tomography have short half-lives (^{11}C, 20 min; ^{13}N, 10 min; ^{15}O, 2 min; and ^{18}F, 110 min), and must be produced within close proximity to the tomographic scanner. In order for positron tomography to be used on a widespread basis it will therefore be necessary to develop accelerator-based radiopharmaceutical production systems that are suitable for use in a large number of hospitals.

There are four companies that are currently actively marketing cyclotrons for the production of short-lived radioisotopes in hospitals. These firms are: The Cyclotron Corporation, Berkeley, CA.; Scanditronix, Inc., Upsalla, Sweden; Japan Steel Works, Tokyo, Japan; and Sumitomo Heavy Industries, Ltd., Tokyo, Japan. Each of these firms has recently announced a new model oriented toward better service of the radiopharmaceutical production needs of positron tomography. Although none of these models have been built and tested at this time, one can compare their features, see Table 1, as described in the commercial literature.

(SPAR) code[25]. From these calculated yields we observed that the use of the p,n reactions on targets enriched in ^{11}B, ^{13}C, ^{15}N or ^{18}O will produce multi-curie levels of activity for a proton beam energy that is reduced by approximately 50% as compared to the smaller medical cyclotrons currently being used. Actually, the yields of ^{13}N, ^{15}O and ^{18}F are higher for the p,n reactions using a 7.5 MeV proton energy on target than for the reactions standardly used with 15 MeV proton or 7.5 MeV deuteron beams[26].

The enriched stable isotope materials are inexpensive and readily available commercially with high enrichments. For example, the cost of thick targets for a 7.5 MeV proton beam will be less than $20 each. The $^{11}B_2O_3$ target can be re-used many times to produce several radiopharmaceutical doses, and it may be possible to develop techniques for the recovery of the other target materials as well.

Reducing the proton energy required of medical cyclotrons for positron tomography by a factor of two would be a significant aid in the ability to use this technique on a widespread basis. However, in order to adequately capitalize on the advantages of the p,n reactions and achieve this reduction in the energy

Table 1

Comparison of Current Compact Medical Cyclotrons

Model	Particles	Energy (Mev)	Current (μA)	No. Targets	Surface Shielding	Computer Control
The Cyclotron Corp. CP-16	p	8-16	100(2)	3-6	yes(1)	yes(1)
	d(1)	4-8	50(2)			
Scanditronix, Inc. RNP-16	p	16	?	2	yes	-
	d	8	?			
Japan Steel Works "Baby"	p	10	50	2	?	-
	d	7	50			
Sumitomo-CGR MeV 325	p	13.5	50	4	yes(1)	-
	d	8	50			
	^3He(1)	in study	40			
	α (1)	16	40			

(1) Optional features.

(2) Where target is outside vacuum, beam current limited to 50 μA protons and 30 μA deuterons due to beam window heating.

Possible Future Developments

Starting with the radiopharmaceutical requirements for positron tomography as they are now understood, we have studied the ways in which new technological approaches in the targetry and radiochemistry components can be used to reduce the size, cost and complexity of cyclotron-based radiopharmaceutical production systems. Since several nuclear reactions can be used for the production of ^{11}C, ^{13}N, ^{15}O and ^{18}F to design an optimum accelerator system, it is desirable as a first step to compare the yields of these reactions as a function of the beam energy and beam current.

We have calculated the yields at saturation for the proton and deuteron induced reactions[24] using the published excitation functions and a computer program that includes the Stopping Power and Ranges

required, it will be necessary to develop specialized beam windows, targetry and activity recovery techniques. While the design of cyclotrons has been highly developed over several decades, the technologies of double foil, gas-cooled beam windows, enriched stable isotope targetry, and automated radiochemistry systems for recovering the target activity and producing short-lived radiopharmaceuticals, have not been equally exploited. The employment of high technology approaches in these areas will result in a large reduction in the requirements of the cyclotron.

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** DISCUSSION **

M. CHAUDRI: Could you tell us please how much activity did you use and what was the time of exposure for this brain scan, vis-à-vis the heart scans?

R. HIGHFILL: The 2-fluoro-2-deoxyglucose is approved by the FDA under an Investigational New Drug application for up to 10 mCi. Due to production problems, however, most of the images shown were made with 3-5 mCi injections. The imaging starts 40 minutes after the injection and requires about 5 minutes per plane. The reason for waiting the 40 minutes is to let the radiopharmaceutical clear from the blood. The heart scans are made in a much shorter period of time although the amount of ^{13}N-ammonia injected is usually less than 20 mCi.

M. HELLER: What are the patient doses from these procedures?

R. HIGHFILL: The whole body dose from the 2-fluoror-2-deoxyglucose is approximately 10 mRad/mCi when the patient voids on schedule. This voiding helps to reduce the dose to the bladder which is the organ that receives the largest radiation exposure.

M. CHAUDRI: Do you have any recirculation problems, especially when you are looking at the heart muscle?

R. HIGHFILL: Yes, and the model applied to interpret the image data must take recirculation into consideration.

J.P. BLASER: Could you give a comparison of sodium iodide detectors with the newly developed wire chamber detectors, which have a lower efficiency but probably much better resolution. How would you judge the differences?

R. HIGHFILL: For coincidence detection of annihilation radiation, where one must detect both 511 keV gamma rays, it is going to be difficult to obtain adequate efficiency from gas chambers. I don't think gas chambers have much potential for this particular application.

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