COMMENTARY

RESEARCH IN THE DEVELOPMENT OF PET RADIOPHARMACEUTICALS

ONE OF THE MAJOR ADVANTAGES OF POSITRON emission tomography (PET) over single photon emission tomography (SPECT) is that the commonly used "PET radionuclides," oxygen-15 (^{15}O), nitrogen-13 (^{13}N), carbon-11 (^{11}C), and fluorine-18 (^{18}F) can be incorporated into molecules of biological interest, or in the case of ^{18}F, into analogs of biological interest. At a recent meeting on radiopharmaceutical development (*1*), the papers presented discussing new positron-emitting radiopharmaceuticals could be grouped into seven general areas—brain receptors, perfusion agents, tumor receptors, myocardial receptors, metabolic agents, labeled drugs, and proteins and antibodies. The major effort in PET radiopharmaceutical development is in the area of agents to study brain receptors. This includes the labeling of specific ligands for a receptor type or subtype, agents that are inhibitors of uptake sites, and agents that are metabolized at specific sites. Agents are being developed for the dopamine, seratonin, norepinephrine, and glucocorticoid receptors. Before these compound s can be applied, the mechanism of uptake needs to be validated, and a mathematical model needs to be developed in order to obtain a quantitative parameter relating either to metabolic rate or the number of receptors, etc.

Michael J. Welch, PhD

The work on agents for the measurement of perfusion is in two general areas. One of these approaches is to develop new generator-produced agents that will quantitate blood flow. In this area copper-62 (^{62}Cu)) (produced from zinc-62) and gallium-68 (^{68}Ga) are the isotopes receiving the most attention. Copper-62 pyruvaldehyde bis(N^4-methythiosemicorbazone) (copper-62-PTSM) has been shown to be useful in the measurement of brain, myocardial, renal, and tumor blood flow, while several ^{68}Ga complexes have been proposed as agents to determine myocardial blood flow. A major challenge to the radiopharmaceutical chemist would be to produce a lipophilic complex of the 75-second half-life rubidium-82 (^{82}Rb), which could cross the blood-brain barrier and quantitate blood flow. Although approaches to this have been discussed (*2*), the rapid preparation of such an agent is still a formidable challenge. The second area of development is the synthesis of a perfusion agent that does not underestimate brain blood flow at high flow rates. Oxygen-15-labeled water, the most commonly used agent for brain blood flow determination, underestimates flow at high flow rate, while labeled butanol accurately reflects flow even at very high flow rates. A major effort is under way to routinely prepare ^{15}O-labeled butanol.

Tumor receptors (estrogen, progestin, and androgen) as well as myocardial receptors (adrenergic, muscarinic, and histamine) are being investigated. Tumor receptor measurement can be used to predict the efficacy of hormonal therapy.

An area of PET research that is likely to increase is the use of PET in the study and evaluation of labeled drugs. Although only five papers were presented in this area during meetings in the United States in 1990, Merck, Sharpe, & Dohme Research Laboratory has organized a meeting on Nuclear Imaging of Drug Discovery, Development, and Approval (*3*) to be held this year. The meeting's organizers have stated that "radiotracers can be used to study the disease process and the effect various drugs or drug candidates have on the disease process, as well as the therapeutic potential of treatments. Thus, it is possible to obtain information noninvasively on the potential efficacy of a candidate drug early in the development stage and to aid in the selection of compounds to be carried further in the development process." The application of radiolabeled drugs (labeled with ^{11}C) or analogs (labeled with ^{18}F) can provide information on drug absorption, distribution, metabolism, elimination, and the specificity of receptor enzyme interactions.

Another area of active research is in the development of ultra compact, simple-to-use accelerators for PET isotope production. The table on page 54N lists some new accelerators that were described at a recent meeting on accelerator targetry and target chemistry (*4*). The goal of these accelerators is either to provide a limited number of radiopharmaceuticals or to use a lightweight accelerator to produce the whole spectrum of positron-emitting radionuclides. These accelerators have several features in common. They are all linear accelerators that are lightweight and have beam currents considerably higher than those generated in a conventional cyclotron. These higher beam currents create challenges in the development of suitable targets for the production of PET radionuclides. If these accelerators can be shown to produce all the PET nuclides, it will make the installation and operation of a PET radionuclide production facility much simpler than is presently possible. The power and cooling requirements are less than for a cyclotron, and the shielding is much lighter in weight. This simplification of a production facility is likely to be a major impetus to the wider use of positron emission tomography.

(continued on page 54N)

Mazziotta Commentary

(continued from page 46N)

ing for nearly a year and was completed on March 15, 1991. The study involved six clinical sites and over 400 individual case studies. Physicians were surveyed pre-and post-scan to determine the effect of the PET results and to determine and quantify patient management decisions as a result of the unique PET information. ICP collected data on the reasons for obtaining PET studies, the pre-scan diagnosis, the ultimate diagnosis, the influence of PET data on diagnosis, other diagnostic testing, as well as any therapy plan and the ultimate outcome. ICP expects to extend this study to longer term evaluations. The four major categories of patients included: patients with dementia, with radiation/chemotherapy necrosis, or with complex partial epilepsy, and those in whom myocardial viability was assessed. The analyses and conclusions of this study will be submitted to a peer-reviewed journal for publication.

Another aspect of the continuing struggle for PET reimbursement has been the lack of independent quantitative data on the true costs of clinical PET. In order to solve this problem, ICP funded an independent assessment of the costs associated with clinical PET by the accounting firm of Coopers & Lybrand. This report which was issued to ICP members during February, represents one of the most comprehensive analyses of clinical PET costs. This report was distributed to numerous medical directors, congressional supporters, and staff personnel at HCFA, OHTA, and the Food and Drug Administration and has become the foundation upon which all discussions of clinical PET costs are based.

The many achievements of ICP have been possible through the efforts of individual physicians from The Society of Nuclear Medicine (SNM), the American College of Nuclear Physicians (ACNP), the American College of Cardiology (ACC), the American College of Radiology (ACR), and the American Academy of Neurology (AAN) as well as interested PET supporters from outside academia. By urging the federal government to begin the regulatory technology assessment process of PET, these individuals have brought PET to its current clinical state.

John C. Mazziotta, MD, PhD
President, Institute for Clinical PET
Professor of Neurology and Radiological Sciences
Vice Chairman of Neurology
UCLA School of Medicine

Welch Commentary

(continued from page 44N)

New Accelerators

Company	Type of Accelerator	Particle(s)	Comment
Ion Beam Applications, Belgium	Cyclone (Cyclone-3)	3 MeV deuterons	^{15}O-only accelerator; Size of a Coke® machine
Science Applications Int'l Corp., San Diego, CA	Radio-frequency quadruple accelerator	8 MeV ^{3}He	With shielding 1/9 weight of cyclotron; ^{15}O and ^{11}C produced carrier added
ACCSYS Technology Pleasanton, CA	Ion linac	Several designs; 3 MeV deuterons 11 MeV protons	Lightweight high current machine
Science Research Lab, Inc. Somerville, MA	Electrostatic accelerator (TCA)	3.7 MeV protons and deuterons	Very high current accelerator; theoretically can produce all PET nuclides at high yield

References

1. Proceedings of eighth international symposium on radiopharmaceutical chemistry, Princeton University, Princeton, NJ, June, 1990. *J Lab Comp in Radiopharm* (in press).

2. Knapp FF Jr., Butler TA, eds. Radionuclide generators new systems for nuclear medicine applications. Washington, DC: American Chemical Society, 1984.

3. International symposium on nuclear imaging in drug discovery, development and approval. Organizer: D. Burns; Merck Sharpe & Dohme Research Laboratory, West Point, PA.

4. Proceedings of the 3rd workshop on targetry and target chemistry, Vancouver, British Columbia, Canada. Ed. T.J. Ruth. December, 1990.

Michael J. Welch, PhD
Professor of Radiation Chemistry in Radiology
Director of the Division of Radiation Sciences
Mallinckrodt Institute of Radiology
Washington University School of Medicine