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RADIOPHARMACEUTICALS IN PET, PROGRESS AND PROMISE

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The PET method is designed to probe human biochemistry and physiology in both normal and pathological states. Its strength lies in the ability to allow the determination or delineation of these biochemical or physiological parameters in a quantitative manner. The technology is driven by the short half-life of the major positron emitters, carbon-11, nitrogen-13 and fluorine-18 and oxygen-15 and their associated radiotracers. Radioisotope generators such as the strontium-82/rubidium-82 parent-daughter, germanium-68/gallium-68 and a number of other potentially useful positron emitters such as bromine-75 can also be considered for PET, but will not be covered in this presentation.

The vitality of PET and its integration into clinical practice will continue to be inextricably related to the advances in chemistry and instrumentation made at the major cyclotron-PET centers and to the rapid transfer of the fruits of basic research and the new high technology to the clinical sector. Currently there is a lag between advances in the basic research arena and their translation into routine clinical practice.

Many of the new radiotracers discussed below are not available for routine use because the automated, robot-operated or remote systems required for their production have not been commercialized. For example, the number of syntheses of carbon-11 and fluorine-18 compounds reported in the literature to mid 1988 were 428 and 240 respectively. The first synthesis of a carbon-11 labeled compound was reported in 1941 and the first synthesis of a fluorine-18 compound in 1967. Yet of all of these compounds reported, only a few of these have seen universal or nearly universal application, e.g. 2-deoxy-2-[^{18}F]fluoro-D-glucose, the various fluorine-18 or carbon-11 labeled butyrophenones, and 6-[^{18}F]-fluorodopa. In the near future the fluorine-18 labeled steroids may see wider applications. In addition to these compounds, oxygen-15 labeled oxygen, water, carbon monoxide and carbon dioxide and nitrogen-13 labeled ammonia are fairly widespread in clinical use.

The major focus to date has been the investigation of the normal and pathological states of the heart and brain including brain tumors. Studies are beginning to appear which encompass other tissues and organs such as lung, liver, pancreas, breast and prostate.

Each organ presents special challenges in the development of suitable labeled compounds designed to probe a specific normal or aberrant biochemical function.

The general aspects of PET and its capabilities have been described in depth in several books (1,2). Chapters on Radiopharmaceuticals in PET can be found in these books (3,4). In addition, a short monograph on the synthesis of positron emitter labeled compounds has also been published (5). A more recent general overview of radiopharmaceuticals for PET (and other aspects of

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PET for purely clinical purposes appeared in recent issues of the Journal of the American Medical Association (6). References to many other articles and reviews can be found in (1-6).

It is the intention of this presentation to focus on the current state of radiopharmaceuticals for PET and where this is leading us.

PET radiopharmaceuticals can be broken down into perhaps seven categories at present with each being applicable to a different aspect of human biochemistry.

(1) Metabolic Probes

At present these constitute a relatively small number of compounds, the most extensively used of which is 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG). Indeed, ^{18}FDG is universally used in both research and clinical practice. In addition to FDG a number of other sugars have been prepared primarily to probe tumor activity. Oxygen-15 (and the necessary adjunctive use of oxygen-15, carbon monoxide and oxygen-15 water) for oxygen utilization must be considered here. Another class of metabolic probes include the amino acids the most common of which is carbon-11 labeled methionine. An emerging series of probes includes growth factors and hormones.

(2) Neurochemical Probes

It is in this area that perhaps the largest number of labeled compounds have been applied. Most of these compounds are designed to bind to receptor sites predominantly the dopamine receptor but also including serotonin norepinephrine, α and β adrenergic, benzodiazepine, opiate, muscarinic, cholinergic, etc. receptors both as agonists and antagonists. In addition compounds which probe reuptake sites and specific carriers must be added to this list.

(3) Enzyme Inhibitors and Enzyme Probes

This area is just beginning to develop as compounds are being synthesized to act as suicide enzyme inhibitors thus allowing the probing of enzyme concentrations in vivo by following the uptake and binding of the labeled compound in a specific enzyme containing site. An alternate approach to enzyme quantitation is to probe the concentration of a metabolically trapped product.

(4) Ion Channel Blockers

The development of cation channel blocker probes especially the calcium channels and the function of NMDA receptors in membrane pore regulation is just beginning and holds considerable promise in being able to monitor the level of cation passage.

(5) Blood Flow Agents

The major agents in use today are oxygen-15 water and nitrogen-13 ammonia. Carbon-11 or oxygen-15 labeled butanol may see more widespread use in the future although increase in radiation exposure to the patient or

temporal constraints in synthesis may mitigate against them relative to the use of simple ^{15}O-tracers.

(6) Ethical Drugs and Radiopharmacology

Although this category relates to a number of the preceding categories, the focus is on the biodistribution and pharmacokinetics of new drugs as assessed by PET. Although drug companies have been slow in applying the PET technique to the study of their new products, the obvious advantages of PET in allowing quantitation in vivo in humans should make this use more prevalent in the future.

(7) Other Positron Emitters

The most common at present are rubidium-82 (from the strontium-82 generator) and gallium-68 (from the germanium-68 generator) and perhaps bromine-75. However, we shall restrict ourselves primarily to carbon-11 and fluorine-18 since these are the most widely used.

NEW RADIOTRACERS FOR PET

Let us turn to some of the agents to be discussed in this presentation. The listing is by no means comprehensive, but merely presents some examples of both progress and promise in this area of nuclear medicine. References are not listed because of space limitations. However, many of the new radiotracers described below were the subject of presentations at the Seventh International Symposium on Radiopharmaceutical chemistry (7).

In metabolic probes, the Julich synthesis of ^{18}FDG has become the current synthesis of choice for this important metabolic probe. In fact, automated synthesis devices utilizing this method are available from Japan Steel Works or Computer Technologies Inc. (CTI). The compound is in routine clinical use in a number of institutions. Fluorine-18 labeled fucose and galactose have been developed as potential tumor imaging agents and their implication in glycoconjugate synthesis explored. Labeled amino acids such as [^{11}C]-DL homocysteine thiolactone as a probe for adenosine in cardiac ischemia, 2-[^{18}F]-fluorotyrosine and a variety of ^{11}C amino acids labeled in various positions for probing protein synthesis have been recently described.

Neurochemicals for probing receptor activity in brain and heart probably constitute the largest class of PET radiopharmaceuticals. Dopamine antagonists have to date been the most popular due to the implication of dopamine in psychotic and neurological illnesses. Thus [^{18}F]spiroperidol and [^{11}C] and [^{18}F] N-methyl spiroperidol have seen extensive use. The benzamide type of receptor antagonists such as ^{11}C-raclopride and its analogs have also been used. More recently focus has expanded to include probing the presynaptic dopamine reuptake mechanism with compounds such as [^{18}F]-GBR13119 (a dialkenylpiperizine) and [N-^{11}C-methyl]nomifensine. Other neurotransmitter receptors are also being probed with agonists and antagonists, i.e. both pre- and post-synaptic response. New benzodiazepine, and histamine receptor active compounds are under study. The steroidal receptors such as the estrogen active compound 16α[^{18}F]fluoroestradiol has been used to image hormone dependent human breast tumors. A ^{18}F-labeled norprogesterone derivative has been postulated as a compound to probe breast tumor growth during anti-

estrogen therapy. Thus the importance in diagnosis and the following of treatment can be materially aided by the use of ever increasing numbers of biologically specific radiotracers being prepared.

Enzyme inhibitors such as ^{11}C-L-deprenyl are being studied as probes for MAO in Parkinson's disease and other disorders.

The study of cation channels with a number of channel blockers such as the ^{18}F-phencyclidines and the drug MK801 labeled with ^{18}F are being used to probe the phencyclidine or the NMDA excitatory amino acid receptors. This is of considerable importance in investigation of brain damage associated with ischemia, Alzheimer's disease and other disorders related to excitatory amino acid receptors.

The focus of this presentation will be on presently used and possibly useful new radiolabeled tracers. It is clear that much work needs to be done in order to establish the utility of any one compound in the diagnosis and evaluation of treatment. However, in their development a great deal of useful biomedical research will have been carried out allowing us to better understand the biochemical basis of human pathology.

The present catalog of useful compounds for PET is small especially in the context of direct clinical utility. Nevertheless, it is clear that the explosion of research in PET radiopharmaceuticals will ultimately lead to new compounds for routine clinical application.

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