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Potential Applications of PET
in
Drug Development

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POTENTIAL APPLICATIONS OF PET IN DRUG DEVELOPMENT

STATEMENT OF OBJECTIVES

The purpose of this continuing education lesson is to increase the participant's knowledge of the unique properties of positron emitting radionuclides and their use in positron emission tomography (PET). Specifically, the participant will be introduced to the application of this modality for the development of new therapeutic drugs.

Upon successful completion of this material, the reader should be able to:

1. describe possible modes of decay for unstable nuclei containing an excess of protons.

2. differentiate between electron capture and positron emission decay.

3. qualitatively describe the process of annihilation of a positron.

4. discuss in general terms the imaging of annihilation photons by coincidence detection using a positron camera.

5. list positron emitting radionuclides which are commonly used in PET.

6. discuss the general steps in the development of new drugs.

7. outline the limitations of classical pharmacokinetic studies in new drug development.

8. describe the attributes of PET which allow for the noninvasive quantitative measurement of drug concentration in human tissues.

9. discuss examples of past applications of PET in drug development and suggest other drug development issues which might appropriately be addressed by using PET.

COURSE OUTLINE

POTENTIAL APPLICATIONS OF PET IN DRUG DEVELOPMENT

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INTRODUCTION

The ability to develop a new drug successfully and bring it to market entails a highly coordinated interaction of numerous groups of individuals working in disciplines ranging from the basic sciences to the legal and medical professions. The basic research aspects involved in drug development include synthetic and medicinal chemistry, pharmacology, molecular biology, physiology, toxicology, biochemistry, as well as others. The components of the process may fall wholly within the drug companies' efforts or in combination with academic institutions and government-sponsored research. It has been estimated that the cost of bringing a new drug to market is in excess of $100 million and the development time-frame can be a decade or longer.[1]

Positron emission tomography (PET) imaging offers unique capabilities for the study of drugs and their effects in living human beings and may provide a means of facilitating drug development. Positron emission tomography offers an opportunity to explore the distribution and concentration of radiolabeled drugs, assess the *in vivo* pharmacologic profile of a drug, and determine various effects the drug may have on tissue metabolism and physiology. In this review, we will describe applications of PET which may aid the drug selection and approval processes.

The current drug development process involves the screening of literally thousands of compounds for desirable pharmacologic activity that may be useful for the treatment of human diseases. This process includes *in vitro* screening, animal testing, and finally, evaluation in humans. Evaluation in humans includes pharmacokinetics, safety and efficacy testing, determination of dosing schedules, as well as evaluations of clinical effectiveness and side effects. The drug selection process, as well as the drug approval process, can be enhanced through the use of PET due to the unique nature of the information PET provides. Unlike x-ray, computed tomography (CT) or magnetic resonance imaging (MRI) which provide primarily anatomical information, PET provides a unique means to make

quantitative measurements of the distribution kinetics of radiolabeled compounds in living animals and humans at levels well below nanogram/cc of tissue. It is therefore possible to study the effects of the drug as well as the body's handling of the drug and physiologic response to it. This monograph will describe how PET may aid the drug development process by citing examples of these approaches.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography makes use of radio-nuclides that decay with the emission of a positron (the antimatter of an electron). These nuclides are produced artificially by bombarding stable nuclei with protons [^{1}H] or deuterons [^{2}H] generating nuclei that are proton-rich. As a result of the proton/neutron imbalance, the nucleus attempts to stabilize by conversion of a proton to a neutron. This conversion occurs by one of two means: (1) electron capture whereby the charge of a proton would be "neutralized" by an orbital electron, or (2) emission of a positive electron (positron) whereby a proton gives up its charge resulting in conversion to a neutron. Positron decay occurs in conjunction with the emission of a neutrino resulting in the reduction of the proton-to-neutron ratio. Positron emitters that are commonly used in PET imaging are listed in Table 1.

When a positron is emitted from the nucleus, it travels a short distance (a few millimeters in tissue), scattering in the surrounding media giving off its kinetic energy and finally interacting with an electron in the absorbing medium. The result of this interaction is annihilation, or the conversion of the mass of both particles into electromagnetic energy according to the laws of modern physics (i.e., $E=mc^2$). Two photons with the energy of 511 keV are given off at an angle approaching 180° to each other to conserve momentum. Current positron cameras, which consist of several hundred detectors arranged in a circular array can determine the location of an annihilation event within the plane of the array, by monitoring events in opposing detectors occurring *coincidentally* or within a predefined time period (on the order of ~15 nanoseconds). Addition of several circular arrays of detectors allows detection of coincident events in more than one plane at a time.

Certain physical principles inherent in the measurement of emitted positrons allows the absolute tracer concentration to be measured as if no overlying tissue were present. This is achieved by measuring the attenuation or absorption of gamma rays from an external positron emitting source of known strength in a manner similar to that of a CT-scanner. The measured attenuation is defined for each image volume (voxel) and a correction is applied to the coincident image to correct for tissue absorption. This information is then reconstructed using standard algorithms (e.g. filtered back projection, maximum likelihood) to give three dimensional tomographic images and, equally important, quantitative and temporal data about the concentration of the radionuclide in the volume (voxel) being imaged.[2]

RADIOCHEMISTRY

Possibly the most significant characteristic of PET in relation to drug development is the availability of positron emitting radioisotopes of carbon (^{11}C), nitrogen (^{13}N) and oxygen (^{15}O). These elements are found in almost all biomolecules and drugs. In addition, fluorine, while not normally a constituent of biomolecules can act as a bio-isostere of hydrogen or the hydroxyl group and is commonly encountered in a variety of drugs. The positron emitting isotope ^{18}F has found widespread application in PET chemistry where it has been used to label biological probes and drugs.[3]

The direct products of most nuclear reactions currently used to prepare positron emitting radionuclides are very simple molecules, such as $^{13}NH_3$, $^{11}CO_2$, or $H^{18}F$. These radiochemicals allow the synthesis of an enormous array of physiologically-active compounds as well as most drugs. Such radiotracers can be used to study enzymes, receptors, and other metabolically-important compounds and their associated reactions. Furthermore, labeling a drug molecule by substituting a stable carbon, nitrogen or fluorine with its positron-emitting isotope yields an authentic tracer, one that is chemically and biologically indistinguishable from the stable or non-radioactive drug. By using such radiotracers, certain unique information about disease processes and therapeutics in living humans can be obtained (which was previously impossible to obtain by any other method).

Although in many cases, incorporation of these building blocks into complex drugs may be straight-forward chemically, the constraints imposed by the short half-lives of the radionuclides often makes radiotracer synthesis a formidable problem. In general, the scheme for radiopharmaceutical preparation must be rapid enough to allow the target drug to be synthesized, isolated, purified and formulated as a sterile, pyrogen-free, isotonic solution within two to three half-lives of the radionuclide. Furthermore, due to the short physical half-lives of most positron-emitting radionuclides, large amounts of radioactivity (usually curies) must be handled, and limiting exposure to personnel is an extremely important consideration. For most drugs, these issues require the design and synthesis of drug precursors that can be radiolabeled in a single step. Over the past several years, these requirements have fostered the development of numerous new methods of rapid remote-controlled and robotics-based chemistry.

Table 1: List of radionuclides commonly used in PET studies.

Radionuclide	Half-life (min.)	Target Reaction	Common Forms
^{15}O	2.0	$^{14}N\ (d,n)\ ^{15}O$	$^{15}O_2,\ C^{15}O_2,\ C^{15}O$
^{13}N	10.0	$^{16}O\ (p,a)\ ^{13}N$	$^{13}NH_3,\ ^{13}N_2$
^{11}C	20.4	$^{14}N\ (p,a)\ ^{11}C$	$^{11}CO_2,\ ^{11}CO,\ ^{11}CH_3I$
^{18}F	110	$^{18}O\ (p,n)\ ^{18}F$	$^{18}F_2,\ H^{18}F$
^{124}I	6048	$^{124}Te\ (d,2n)\ ^{124}I$	$Na^{124}I$
^{82}Rb	1.3	^{82}Sr decay (T1/2;25 d)	$^{82}RbCl$

Table 2: Advantages of PET Measurements of Pharmacokinetics.

- Almost any drug tracer can be prepared with ^{13}N, ^{11}C, ^{15}O or ^{18}F

- Absolute quantitation

- High resolution: 3.5 - 5 mm

- High specific activity radiolabeling (5,000-15,000 mCi / mmole) limits physiological or pharmacological side effects

- Radiation dosimetry favors repeat studies

- Repetitive measurements possible after physiological or pharmacological interventions due to short half-lives

- Applicable to studies in humans

ADVANTAGES AND LIMITATIONS OF PET MEASUREMENTS

Compared with standard methods employed for the study of new drugs, PET techniques have many clear and important advantages (Table 2). Since there are positron emitting radionuclides of nitrogen, oxygen, carbon and fluorine, a PET tracer can be prepared for almost any drug. Due to the quantitative nature of PET measurements, the tissue concentrations of a drug determined by imaging are nearly identical to the results of direct measurements of radioactivity in tissue samples. The image resolution of PET permits measurements in small volumes of tissue (< 1 cc). The short physical half-lives of most PET tracers result in relatively low radiation dosimetry which allows for repetitive measurements in a single subject after physiologic or pharmacologic interventions. Due to the high specific activities of most PET tracers, physiologic and pharmacologic effects are negligible. Most importantly, almost all PET radiopharmaceuticals that are developed for studies in animals can be directly applied to investigations in normal human volunteers and patients. In fact, due to larger body size, PET studies in humans tend to be more accurate.

In addition to these advantages, the short physical half-lives of the more useful radionuclides (^{11}C, ^{13}N, ^{15}O, and ^{18}F) also present several limitations.

- The radioactive drug must be prepared separately for each subject at an "on site" cyclotron/radiochemistry facility. This limits the general availability of these compounds to specialized facilities at large hospitals and universities.
- The time interval over which pharmacokinetic studies can be performed is limited. In general, this time frame is approximately four times the physical half-life of the tracer, approximately 8 min. with ^{15}O, approximately 40 min. with ^{13}N, approximately 80 min. with ^{11}C, and approximately 8 hours with ^{18}F. Clearly, this is less of a problem with ^{76}Br and ^{124}I.
- The number of chemical manipulations that can be used to prepare PET radiopharmaceuticals must be minimized to obtain sufficient radiochemical product.

POTENTIAL APPLICATIONS IN DRUG DEVELOPMENT

One way to categorize potential applications of PET in drug development is in relation to the available radiotracers that may be employed for each application. The types of studies possible for the evaluation of new drugs relies on the types of radiotracers available. We may want to know where the drug is, what the drug is binding to, how the drug effects normal tissue function or how well the drug is working. Knowledge of the behavior of a drug can be determined using the radiolabeled drug of interest (DOI) or radiolabeled pharmacologic, metabolic or physiologic probes. Each may be answered depending on (a) the radiotracers available to the investigator/clinician and (b) the experimental design possible. In the following sections, applications of PET in drug development will be outlined based on the specific type of radiotracer used. Table 3 lists examples of radioligands that have been used for PET imaging. Finally, pharmacokinetic studies of new antimicrobials performed with PET will be discussed in some detail.

RADIOLABELED DRUG OF INTEREST

The availability of the radiolabeled DOI enables the investigator to determine the biodistribution or pharmacokinetics and target tissue in normal organs as a function of time and dosage. In this case, the DOI is radiolabeled and the organ distribution and kinetics are determined either at the tracer level (extremely small mass) or after co-administration of non-radioactive drug (usually at a dose expected to be used therapeutically).

Classic pharmacokinetic parameters obtained from animal models may not be relevant to the human experience which may cause initial dose estimates to be inaccurate. This could result in sub-therapeutic or potentially toxic clinical trials, thus, wasting time and money in the early phases of drug evaluation. Adding radioactive DOI to the unlabeled DOI formulation allows conversion of the drug concentration in the plasma to specific organ concentrations. This is done by simultaneously measuring the plasma drug concentration, either conventionally or by isotope dilution techniques and measuring drug concentration in various organs and tissues from the PET image data. This cross calibration can then render a meaningful therapeutic plasma level which will correspond to an optimal concentration for each organ system or tissue without relying on animal pharmacokinetic studies.

The success of drug therapy is thought to be directly related to the drug concentration at the site of action (e.g., antibiotics at the site of infection). However, pathophysiologic changes in tissues may alter the delivery of drugs, making extrapolations from normal tissue data unreliable. Using radiolabeled DOI enables the determination of tissue concentrations or pharmacokinetics under conditions of various disease states. PET imaging of the DOI in patients with various pathologies can determine the effect specific pathologies have on drug delivery and residence times. Such information can then be used to tailor dose schedules in

Table 3: Examples of radioligands that have been used for PET imaging.

RECEPTOR	LIGAND	SPECIFICITY	REFERENCE
Dopamine	^{11}C - SCH-23390	D$_1$	(48)
	^{11}C - SCH-39166	D$_1$	(49)
	^{11}C - Methylspiperone	D$_2$, (5HT$_2$)	(50)
	^{76}Br - Bromospiperone	D$_2$, (5HT$_2$)	(51)
	^{11}C - Raclopride	D$_2$	(52)
	^{76}Br - Bromolisuride	D$_2$	(53)
Serotonin	^{18}F - Setoperone	5HT$_2$	(54)
	^{11}C - Methylbromo LSD	5HT$_2$	(55)
Benzodiazepine	^{11}C - Flumazenil	BZ$_1$, BZ$_2$	(56)
	^{11}C - PK11195	Peripheral	(57)
Opioid	^{11}C - Carfentanil	μ	(58)
	^{11}C - Diprenorphine	μ, k	(59)
	^{18}F - Acetylcyclofoxy	μ	(60)
Acetylcholine	^{11}C - MQNB	M$_1$, M$_2$	(61)
(muscarinic)	^{11}C - Levetimide	M$_1$, M$_2$	(62)
	^{11}C - Scopolamine	M$_1$, M$_2$	(63)
Adrenergic	^{11}C - CGP 12177	ß$_1$, ß$_2$	(64)

patients. For example, using ^{11}C labeled phenytion (^{11}C DPH), regional brain concentrations were determined in patients with medically-resistant epilepsy. The concentration of ^{11}C DPH was not significantly different within the epileptogenic focus as compared to corresponding drug levels in normal brain areas. These findings support the idea that the medically-resistant intractable epilepsy is not due to a pharmacokinetic cause (i.e. poor drug delivery at the site of the epileptogenic focus), but rather a pharmacodynamic-based resistance.[4]

It is also possible to compare the pharmacokinetics of a drug given by different routes of administration. The pharmacokinetic profiles of BCNU were compared after intravenous administration and intra-arterial administration using ^{11}C BCNU in patients with recurrent gliomas. Using intra-arterial administration, BCNU levels in tumors averaged fifty-fold greater than comparable intravenous administration. The authors suggest that, within this small group of patients (n = 10), the degree of metabolic trapping of BCNU in tumors correlated with the clinical response to this agent.[5]

If the DOI is receptor specific, it is possible to determine receptor binding parameters (affinity and capacity) using radiolabeled DOI in living human beings. This can be accomplished through Scatchard-type experiments, whereby high specific activity radiolabeled DOI is administered with increasing amounts of unlabeled DOI. Measuring the concentration of radiolabeled DOI in an anatomically-specific area of interest in the presence of increasing concentrations of nonradioactive drug allows the calculation of receptor affinity as well as the maximal binding concentration of the DOI.[6] This data should be useful in the determination of dosing, particularly for neuroleptic drugs. If maximal therapeutic effect can be demonstrated to occur at a known level of receptor occupancy, and that degree of occupancy can be related to a given dose level, then increasing doses above the level will most likely result in increased incidence of side effects without further therapeutic benefit.

It is also possible to determine the extent of inter-action of competing drugs on the pharmacokinetics and tissue concentration of the DOI. In this case, the DOI is radiolabeled and the organ distribution and kinetics are determined before and after the administration of a non-radioactive drug with a particular pharmacologic profile. In this manner it may be possible to determine the receptor affinity of a novel neuroleptic (DOI) in the presence of a well characterized drug having similar pharmacology. Such information may be of interest to drug companies and the FDA when trying to evaluate "me-too" type drugs.

RADIOLABELED PHARMACOLOGIC PROBES

For the sake of this discussion, a pharmacologic probe is a ligand which displays a unique localization/accumulation within specific areas of the body in relation to the pharmacologic characteristic of the ligand. For example, C-11- Sch 23390 selectively binds to dopamine- D_1 receptors in the brain. By following accumulation or displacement of this ligand after administration of a DOI it should be possible to describe a characteristic of the DOI in relation to dopamine D_1 pharmacology.

The availability of radiolabeled pharmacologic probes (such as those for the dopaminergic system)[7] allows for the determination of subtype-specific receptor occupancy and residence time of drugs as a function of dose and dosing schedule. This may be achieved by determining the maximal uptake of radiolabeled probe at the receptor site prior to administration of DOI, then administering unlabeled candidate drug at various dosage levels and times prior to the injection of a subsequent tracer dose of radiolabeled pharmacologic probe. Assuming no physiologic changes occur which would hamper the delivery and binding of the probe to the receptor system, then the difference in concentration of probe at the receptor site, before and after administration of the DOI, indicates the extent to which the DOI occupies that receptor. If after a single dose of DOI the receptor site remains occupied (i.e., the radiolabeled probe does not accumulate at the receptor site) for 24 hours at a level thought to be therapeutic, the drug may need to be administered only once a day. If the occupancy drops in four hours to levels thought to be sub-therapeutic, the drug may need to be administered several times a day. Such information should lead to optimal dose scheduling as well as characterization of therapeutic ratio.[8]

For example, ^{11}C-labeled SCH 23390, a dopamine D_1 specific radioligand, was used to study D_1 receptor occupancy after an 80 milligram oral administration of a new benazepine, NNC756, in three men. D_1 receptor occupancy was 75%, 66% and 47% after 1.5 hours, dropping to 46%, 36% and 24% at 7.5 hours. The occupancy at 1.5 hours was similar to that shown to induce effects in animal models for prediction of antipsychotic effects. Restlessness appeared in two of the subjects at the time of peak drug plasma levels. This study confirmed that an 80 milligram dose resulted in a percent occupancy level which should be appropriate for investigation of the potential anti-psychotic effects of NNC756.[9]

Radiolabeled pharmacologic probes also allow other fundamental studies to be performed which may help elucidate the mechanism of action of some drugs. For example, pharmacologic parameters may also be measured by probing systems with receptor subtype-

specific ligands.[10] An example of this approach was the evaluation of the dopamine D_2 and D_1 receptor binding characteristics of the atypical neuroleptic, clozapine, using ^{11}C raclopride and ^{11}C SCH 23390 as test ligands for D_2 and D_1 receptors, respectively.[10-14]

RADIOLABELED PHYSIOLOGIC AND METABOLIC PROBES

Radiolabeled physiologic and metabolic probes enable the investigator to perform pharmacodynamic evaluation of candidate drugs. A variety of radiolabeled substrates are available allowing the measurement of physiologic and biochemical phenomena such as blood flow, oxygen consumption, blood volume, amino acid metabolism, DNA synthesis, glucose metabolism, oxidative metabolism in the TCA cycle, fatty acid metabolism, and protein synthesis rates.

Much can be learned about a candidate drug by measuring its effect on physiologic parameters and biochemical processes. For example, several fluoroquinolone antibiotics have been evaluated for their ability to alter cerebral blood flow, glucose metabolism and oxygen consumption.[15,16] By measuring cerebral blood flow and glucose utilization before and after drug administration, a profile of the drug effect on normal tissue can be generated. While such effects are not related to efficacy of the drug of interest, it allows the exploration of physiologic parameters which may well aid in the detection of side effect profiles and at what dose levels these side effects are likely to occur.

Another use would be looking at efficacy by monitoring the downstream effect of a therapeutic agent. For example, fluorodeoxyglucose ([18]FDG) has been shown to be an indicator of tumor viability and aggressiveness.[17] Monitoring the effectiveness of a new anti-cancer drug may be done by measuring FDG metabolism in tumors before and after therapeutic dosing of novel chemotherapeutics. This could eventually become a more sensitive and direct assay of response than waiting to calculate survival rates. Particularly, it would alert investigators if there was no effect on the tumor, thus, indicating therapeutic failure. Such rapid turnaround of a therapeutic trial could save time and money with the added benefit of potentially saving lives by highlighting potential therapeutic failure. FDG has also been applied to the assessment of the therapeutic effectiveness of anti-arthritis drugs.[18]

Pharmacology can be studied indirectly using physiologic and metabolic probes, as in the case of serotonin (5HT) pharmacology. The pharmacology of serotonin receptors has been characterized in a number of PET studies using [18]FDG as a marker of regional cerebral glucose utilization. In healthy subjects, the 5HT re-uptake blocker, fluoxetine was shown to reduce regional cerebral metabolic glucose metabolism in limbic areas of the brain.[19] In patients suffering from obsessive compulsive disorders, chronic administration of the 5HT re-uptake blockers, fluoxetine or chlomipramine, ameliorated the excessive symptomatology and normalized abnormally-elevated regional cerebral glucose metabolism. Fenfluramine, a 5HT anorectic, increased regional cerebral glucose metabolism[20] and regional cerebral blood flow[21] in the pre-frontal cortex and decreased these metabolic activities in the occipital areas. These regions are thought to be involved in excessive compulsive disorders.

Using ^{15}O-labeled water as a measure of regional cerebral blood flow, it was found that buspirone (a 5HT agent with anxiolytic and anti-depressant activities) increased task-related regional cerebral blood flow in the left pre-frontal and in the retro splenial/parahippocampal cortex.[22] The latter is a brain region with high $5HT1_A$ receptor density.[23]

PHARMACOKINETICS OF ANTIMICROBIALS

To provide a more comprehensive example of the application of PET to the study of drug development, the discussion will now focus on a particularly promising application of PET: the measurement of pharmacokinetics of new drugs. For a more in-depth discussion of the mathematical models involved in the analysis of pharmacokinetic data, the reader is referred to a review by Ponto and Ponto.[24,25]

Fluconazole [2-(2,4-diflorophenyl)-1,3,1-bis)1H-1,2,4-triazole-1-yl(-2-propanol] is the first of a new class of synthetic antifungal agents[26-28] which acts by inhibiting fungal cytochrome P-450 sterol 14-C α-demethylation, which results in depletion of normal fungal sterols and accumulation of 14 α-methyl sterols.[29-32] The use of fluconazole for treating invasive fungal infections caused by organisms such as: *Cryptococcus neoformans, Candida species, Coccidioides immitis, Histoplasma capsulatum,* and *Blastomyces dermatitidis,* has been a major advance in antimicrobial chemotherapy.[33] The broad spectrum fungistatic action of fluconazole in conjunction with its low systemic toxicity and favorable pharmacokinetic profile has made this drug a particularly attractive therapeutic agent. The use of fluconazole for the primary treatment of disseminated cryptococcal infections in AIDS patients and life threatening fungal infections in immuno-compromised hosts, however, has remained a controversy. At issue is the establishment of optimal dosing schedules and actual concentrations of drug delivered to specific tissues, particularly the site of infection.

Although the tissue distribution of fluconazole in laboratory animals has been reported[34,35] and

concentrations of drug in body fluids of humans have been measured,[36-40] detailed studies of tissue concentrations in humans are lacking. Fluconazole contains two fluorine atoms which make it an ideal candidate for radiolabeling with ^{18}F. Fluconazole undergoes minimal metabolism *in vivo* and hence the measurement of radioactivity in tissue and blood should be an accurate reflection of the concentration of the intact drug in these tissues. The synthesis of ^{18}F-fluconazole required a novel precursor in order to introduce the ^{18}F at a late stage of the synthesis so that the overall preparation time was suited to the physical half-life of ^{18}F. Standard methods of fluconazole synthesis were not feasible because both fluorine atoms are introduced at an early stage of the synthesis. Radiochemical synthesis yields pharmaceutical grade ^{18}F fluconazole which is identical both chemically and in terms of antimicrobial activity to the usually-prescribed drug, except that one of the fluorine atoms is the positron-emitting ^{18}F isotope.[41]

In preliminary studies, this radiopharmaceutical was used to measure the pharmacokinetics of fluconazole in normal rabbits and rabbits with candidal infections using PET methodology.[42] These studies showed that when ^{18}F-fluconazole was administered as a tracer in conjunction with therapeutic amounts of authentic fluconazole, a uniform distribution of drug throughout the uninfected tissues of the body was seen with the exception of the liver. In the liver, concentration of the drug was two-to-threefold higher than in other tissues. It was of interest to note in this study that when ^{18}F-fluconazole was injected without therapeutic doses of the unlabeled compound, there was a distinct difference in the distribution of the tracer indicating a less uniform distribution throughout the animal and higher concentrations in the liver. The reason for this difference remains unclear. However, the importance of this study was to demonstrate that PET scanning with ^{18}F-labeled fluconazole can be used to measure drug concentrations non-invasively *in vivo*. The ^{18}F -fluconazole PET data was similar to those reported with a single dose of ^{14}C-labeled fluconazole infused into mice and analyzed with whole body autoradiographic studies.[34]

Further studies with ^{18}F fluconazole were carried out in healthy human subjects. Volunteers were injected with a tracer dose of ^{18}F fluconazole plus 400 milligrams of unlabeled drug and studied over a two-hour period. The PET studies showed that there was significant distribution of the radiolabeled drug in all organs studied with nearly constant levels achieved by one hour. Plateau concentrations of fluconazole in key organs (micrograms per gram of tissue) included the following: whole brain 4.92 ± 0.17, heart 6.98 ± 0.2, lungs 7.81 ± 0.46, liver 12.9 ± 0.24, spleen 22.96 ± 2.5, kidney 11.23 ± 0.61, prostate 8.24 ± 0.58 and blood 3.76 ± 0.3. Based on this PET data, predictions could be made as to

the dosage needed for antifungal therapy where the effective concentration of drug for a given microbe was known.

It was also of interest to note that the pharmacokinetic data acquired in rabbits with ^{18}F-fluconazole was significantly different in certain tissues compared to humans. Hence, direct application of animal pharmacokinetic data to humans must be done with caution. This suggests that PET imaging of drug deposition in humans is an important tool for the study of pharmacokinetics in humans.

Positron emission tomography has also been applied to the study of a novel fluoroquinolone antibiotic, fleroxacin [6,8-difluoro-1,4-dihydro-1-(2-fluoroethyl)-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinolinecarboxylic acid]. PET and ^{18}F-labeled fleroxacin have been used to study the pharmacokinetics of fleroxacin in rabbits with *E. coli* infections[43] as well as the pharmacokinetics in healthy human subjects. In rabbits with *E. coli* infection, accumulation of the radiolabeled drug in infected and healthy thigh muscles were similar. Peak concentrations of the drug of more than three times the minimum inhibitory concentration (MIC) for 90% of members of the family Enterobacterciae were measured in all tissues except the brain, and these concentrations remained above this level for more than two hours. Especially high peak concentrations were achieved in the kidney, liver, blood, bone and lung. These data indicate that fleroxacin should be particularly useful in treating gram-negative infections involving these tissues. In contrast, the low concentration of drug levels in the brain should limit the toxicity of the drug in the central nervous system

Fleroxacin-F18 and PET were also used to study the pharmacokinetics of the nonradioactive (unlabeled) drug in 12 healthy volunteers.[44] ^{18}F-fleroxacin was administered with a therapeutic dose of unlabeled fleroxacin, and serial PET images and blood samples were acquired for eight hours beginning at the start of the initiation of the infusion of the nonradioactive drug. The subjects were subsequently treated with unlabeled drug for three days, and on the following day, infusion of radiolabeled drug, PET imaging, and blood collection were repeated. PET imaging showed that there was a rapid accumulation of radiolabeled drug in most organs, with stable levels achieved within one hour after completion of the infusion. Especially high levels of drug were found in kidney, lung, myocardium, and spleen. Peak concentrations of drug, more than two times the MIC for 90% of Enterobacterciae strains, were achieved in all tissues except the brain, and remained above this level for more than six to eight hours. Concentrations of fleroxacin were similar in males and females and before and after pre-treatment with unlabeled drug. Table 4 shows the plateau concentrations in several tissues

Table 4: Plateau concentrations of fleroxacin in several tissues measured between 2 to 8 hour after infusion in micrograms per gram (plus or minus the standard area of the mean) as measured by F-18-labeled-fleroxacin and PET in healthy human subjects (from ref. 44).

Organ	Plateau Concentrations	
	Micrograms per gram	Standard Error of the mean
Brain	0.83	0.032
Myocardium	4.53	0.24
Lung	5.80	0.48
Liver	7.31	0.33
Spleen	6.00	0.47
Bowel	3.53	0.74
Kidney	8.85	0.64
Bone	2.87	0.29
Muscle	4.60	0.33
Prostate	4.65	0.48
Uterus	3.87	0.39
Breast	2.68	0.11
Blood	2.35	0.09

measured between two to eight hours after infusion [in micrograms of drug per gram of tissue (plus or minus the standard area of the mean)] as measured by ^{18}F-fleroxacin and PET in healthy human subjects. These studies demonstrate the utility of ^{18}F-fleroxacin and PET for determining pharmacokinetics in humans, and confirm the findings of earlier studies of ^{18}F-fleroxacin in animals.

SUMMARY

Over the past several years, there has been a large body of data accumulated on the use of PET for the study of drugs.[45] Previously, pharmacokinetics and drug dosing has relied upon the measurement of blood and urinary concentrations of drugs in humans combined with the tissue distribution data provided by animal experiments. The ability to correlate conventional pharmacokinetic parameters such as blood levels and urinary excretion with drug tissue concentrations obtained from imaging techniques such as PET will provide great potential for defining appropriate dosing schedules and, therefore, facilitation of drug development.[46]

Also, issues related to mechanisms of action of new drugs, especially receptor-mediated agents such as novel antidepressants or antipsychotics acting on a variety of neurotransmitter receptors,[47] can be characterized directly and indirectly with PET techniques.

In summary, PET allows unique investigations of drugs in the human body. Positron emission tomography may play an increasing role in the FDA's drug approval process based on the ability of PET to provide an accurate objective assessment of drug behavior *in vivo*.

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QUESTIONS

1. Unstable nuclei containing an excess of protons decay by:

   a. emission of an electron
   b. capturing an electron from an inner shell
   c. emission of a positron
   d. either by emission of a positron or capture of an electron

2. The range of an emitted positron in tissue is a few:

   a. nanometers
   b. micrometers
   c. millimeters
   d. centimeters

3. A positron annihilates:

   a   immediately upon being emitted form the nucleus
   b. upon interaction with an electron in the scattering medium
   c. upon interaction with a neutrino
   d. upon interaction with another positron in the scattering medium

4. The half-lives of positron emitting radionuclides used in PET range form a few:

   a. seconds to a few minutes
   b. minutes to a few hours
   c. hours to a few days
   d. days to a few weeks

5. The specific activity of PET radiopharamaceuticals is generally:

   a. low compared Tc-99m labeled radiopharmaceuticals
   b. very high compared to Tc-99m labeled radiopharmaceuticals
   c. about the same as Tc-99m labeled radiopharmaceuticals
   d. not of major concern for this class of radiopharmaceuticals

6. Fluorine-18 is commonly used in PET because:

   a. it can be substituted for a OH or H in a molecule
   b. it has a relatively long half-life
   c. many drugs contain a native fluorine atom
   d. all of the above

7. Quantitative measurement of drug concentration in human tissues with PET is possible in part because:

   a. positron emitting radionuclides decay with high energy photons
   b. tissue attenuation and scattering can be corrected for
   c. physical half lives are relatively short
   d. b & c above

8. An important property of a positron emitting version of a new neuroreceptor binding drug is:

   a. the use of the radionuclide with the shortest possible half life
   b. the use of the radionuclide with the longest possible half life
   c. a radiopharmaceutical with the lowest possible specific activity
   d. a radiopharmaceutical with the highest possible specific activity

9. The application of PET in drug development has included:

   a. radiolabeling the drug itself with C-11
   b. radiolabeling the drug itself with F-18
   c. using F-18 FDG as a metabolic probe
   d. all of the above

10. The preparation of PET radiotracers for drug development :

   a. usually only requires a single step addition of the radionuclide
   b. can be accomplished in the nuclear pharmacy using existing equipment
   c. often requires novel synthetic chemistry in which the radionuclide is added late
   d. does not include quality control tests due to the half-life of the radionuclides

11. One major disadvantage of the use of PET in drug development is the short physical half-lives of the radionuclides which:

   a. do not allow for repeat studies
   b. requires the use of Curie quantities of starting material
   c. do not allow for regional distribution
   d. results in relatively high radiation absorbed doses

12. A physiologic probe which has been used to monitor the antiinflammatory properties of a new drug is:

   a. N-13 Ammonia
   b. C-11 Acetate
   c. F-18 FDG
   d. F-18 fleroxacine

13. Applications of PET in drug development include:

    a. measurement of changes in tissue concentration over time
    b. comparison of serum levels to tissue levels of drug
    c. optimizing dosing schedules
    d. all of the above

14. To date, the use of PET in the development of antibiotics has been limited to:

    a. antifungal agents
    b. drugs with a N-methyl group in its structure
    c. drugs with a fluorine atom in its structure
    d. drugs intended for use in the CNS

15. An example of a pharmacologic probe which could be used to evaluate a new benzapine drug is a :

    a. F-18 labeled FDG
    b. C-11 labeled D1 neuroreceptor ligand
    c. N-13 ammonia
    d. C-11 labeled 5HT receptor ligand

16. The actual tissue concentration of a drug (μg/cc) in human tissue can be measured with a PET camera and a PET radiotracer when which of the following are known:

    a. camera calibration in cpm /μCi
    b. specific activity of the radiotracer
    c. administered activity in mCi
    d. a & b above

17. Image resolution for modern PET imaging systems is:

    a. lower than SPECT systems at 1 cm
    b. lower than SPECT systems at .5 cm
    c. higher than SPECT systems at 5 mm
    d. higher than SPECT systems at 1 mm

18. In a study of the receptor occupancy of a new neuroleptic drug (containing F, C, O, and N) in which a normal subject will be studied with a PET radiotracer before and after an intravenous injection of the authentic drug, the most convenient radionuclide for labeling this drug is

    a. F-18 because it has the longest half-life
    b. C-11 because it allows for repeat studies on the same day
    c. O-15 because it allows for the administration of 100 mCi doses
    d. N-13 because a 10 minute half life is ideal

19. The pharmacokinetics of a PET radiotracer labeled with F-18 can be studied for approximately:

    a. 2 hours
    b. 4 hours
    c. 6 hours
    d. 8 hours

20. The development of new cancer chemotherapy agents can be expedited by the use of PET by:

    a. using radiolabeled versions of all prospective new agents
    b. using F-18 FDG to monitor individual patient response to a specific drug
    c. using O-15 water to monitor tumor blood flow
    d. using C-11 acetate as a metabolic probe

21. PET has been used to monitor the effectiveness of fluoxetine in patients with Obsessive Compulsive Disorder by:

    a. radiolabeling fluoxetine with F-18
    b. measuring regional cerebral glucose metabolism with F-18 FDG
    c. measuring regional cerebral blood flow with O-15 water
    d. b & c above

22. The use of PET is especially valuable in the development of antimicrobial drugs because:

    a. all antimicrobials contain a fluorine atom in their structure
    b. antimicrobial drugs are uniformly distributed throughout the body
    c. tissue levels of the drug can be matched to microbe inhibitory concentrations
    d. antimicrobial agents are excreted unchanged

23. The use of PET determining effective dosing schedules for new drugs is possible by:

    a. preparing radiolabeled oral dosage forms of the drug
    b. measuring urinary excretion of the PET radiotracer
    c. comparing blood and urine levels to tissue concentration of the drug
    d. measuring the concentration of metabolites in the blood

24. One area of drug development which is especially suited to the use of PET is with drugs which:

    a. act by enzyme inhibition
    b. interact with neurotransmitters in the brain
    c. do not cross the blood brain barrier
    d. are highly bound to plasma proteins

25. The overall goal of using PET in drug development is:

    a. increase the number of potential new drugs
    b. decrease the time and cost of new drug development
    c. decrease the incidence of adverse reactions to new drugs
    d. elaborate the mechanism of action of new drugs