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REVIEW ARTICLE

Overview of positron emission tomography chemistry: clinical and technical considerations and combination with computed tomography

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Summary

The concept of emission and transmission tomography was introduced by David Kuhl and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed by Michel Ter-Pogossian, Michael E. Phelps and others at the Washington University School of Medicine.

Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a 3-dimensional image or map of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in 3-dimensional space within the body are then reconstructed by computer analysis. In modern scanners, this reconstruction is often accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine. If the biologically active molecule chosen for PET is 18F-fluorodeoxyglucose (FDG), an analogue of glucose, the concentrations of tracer imaged give tissue metabolic activity in terms of regional glucose uptake. Although use of this tracer results in the most common type of PET scan, other tracer molecules are used in PET to image the tissue concentration of many other types of molecules of interest.

The main role of this article was to analyse the available types of radiopharmaceuticals used in PET-CT along with the principles of its clinical and technical considerations.

Key words: clinical applications, pharmaceuticals, positron emission tomography

PET radiopharmaceuticals

PET radiopharmaceuticals are uniquely different from SPECT (single photon emission computer tomography) radiopharmaceuticals. The most common PET radionuclides are 11C, 15O, 13N, 18F, and 82Rb, which are short-lived and put limitations on the synthesis time for PET radiopharmaceuticals and their clinical use. The attractive advantage of PET radiopharmaceuticals is that the ligands used in radiopharmaceuticals are common analogs of biological molecules, and therefore often depict a true representation of biological processes after *in vivo* administration. FDG is an analog of glucose used for cellular metabolism and $H_2{}^{15}O$ for cerebral perfusion.

Many radiopharmaceuticals have been used for PET imaging; however, only a few are routinely utilized for clinical purposes. Almost all of them are labeled with one of the 4 common positron emitters: 11C, 13N, 15O, and 18F. Of the 4, 18F is preferred most, since it has a relatively longer half life ($t1/2 = 110$ min) that allows its supply to remote places. In all cases, a suitable synthesis method is adopted to provide a stable product with good labelling yield, high specific activity, high purity, and most importantly, high *in vivo* tissue selectivity. 82Rb is used as a PET radiotracer in the form of 82Rb-RbCl that is available from the 82Sr-82Rb generator. The following is a description of the syntheses of the common clinically used PET radiopharmaceuticals and a few with potential for future use.

18F-sodium fluoride

Fluorine-18 ($t1/2$=110 min) is produced by irradiation of 18O-water with 10-18MeV protons in a cy-

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clotron and recovered as 18F-sodium fluoride by passing the irradiated water target mixture through a carbonate type anion exchange resin column. The water passes through, whereas 18F- is carbonate solution. Its pH should be between 4.5 and 8.0. While 18F-sodium fluoride is most commonly used for the synthesis of 18F-fluorodeoxyglucose, it is also used for other 18F-labeled PET radiopharmaceuticals. The U.S. FDA has approved it for bone scintigraphy, since it localizes in bone by exchanging with PO4- ion in the hydroxyapatite crystal.

18F-2-fluoro-2-deoxyglucose (2-FDG) is normally produced in places where a cyclotron is locally available. Its molecular formula is C8H11 18FO5 with molecular weight of 181.3 daltons. 18F-2-FDG can be produced by electrophilic substitution with 18F-fluorine gas or nucleophilic displacement with 18F-fluoride ions. The radiochemical yield is low with the electrophilic substitution, so the nucleophilic displacement reaction has become the method of choice for 18F-2-FDG synthesis. Deoxyglucose is labelled with 18F by nucleophilic displacement reaction of an acetylated sugar derivative followed by hydrolysis [1]. In nucleophilic substitution, a fluoride ion reacts to fluorinate the sugar derivative. A solution of 1, 3, 4, 6-tetra-*O*-acetyl-2-*O*-trifluoromethane-sulfonyl-b-D-mannopyranose in anhydrous acetonitrile is added to a dry residue of 18F-fluoride containing aminopolyether (Kryptofix 2.2.2) and potassium carbonate (Figure 1).

Kryptofix 2.2.2 is used as a catalyst to enhance the reactivity of the fluoride ions. The mixture is heated under reflux for about 5 min. The solution is then passed through a C-18 Sep-Pak column, and acetylated carbohydrates are eluted with tetrahydrofuran (THF), which are then hydrolyzed by refluxing in hydrochloric acid at 130° C for 15 min. 18F-2-fluoro-2-deoxyglucose (2-FDG) is obtained by passing the hydrolysate through a C-18 Sep-Pak column. The yield can be as high as 60%, and the preparation time is approximately

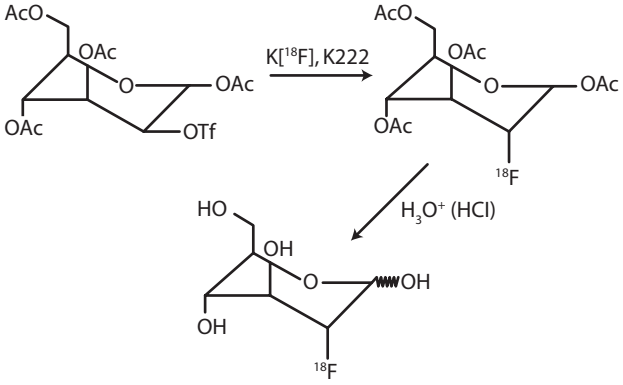

Figure 1. The structure of 18F-Sodium Fluoride.

50 min. The final solution is filtered through a 0.22 mm filter and diluted with saline, as needed. It should have a pH of 7.0. Since Kryptofix 2.2.2 is toxic [3] causing apnea and convulsions, modifications have been made to substitute it with tetrabutylammonium hydroxide or bicarbonate, which have been adopted by many commercial vendors. Also, in some other methods, the C-18 Sep-Pak column separation has been eliminated so as to carry out the acidic hydrolysis in the same vessel. In methods where Kryptofix 2.2.2 is still used, several Sep-Pak columns are used to separate Kryptofix 2.2.2 and reduce it to practically a negligible quantity. 18F-2-FDG is used primarily for the study of metabolism in the brain and heart, and for the detection of epilepsy and various tumors. In metabolism, 18F-2-FDG is phosphorylated by hexokinase to 2-FDG-6-phosphate which is not metabolized further.

6-18F-L-fluorodopa

Like 18F-2-FDG, 6-18F-L-fluorodopa is also produced in places where a cyclotron is available locally. There are several methods of synthesising 6-18F-fluoro-3,4-dihydroxyphenylalanine (6-18F-L-fluorodopa), of which the method of fluorodemetallation, using electrophilic fluorinating agents, is most widely used. Electrophilic reactions involve the reaction of fluorine in the form of F+ with other molecules. Only the L-isomer of dopa is important, because the enzymes that convert dopa to dopamine, which is targeted by the radiopharmaceutical, are selective for this isomer. Initially, a suitably protected organomercury precursor (N-[trifluoroacetyl]-3, 4-dimethoxy-6-trifluoroacetoxymercuriophenylalanine ethyl ester) of dopa is prepared. [18F]-labelled acetylhypofluorite prepared in the gas phase is then allowed to react with the mercury precursor in chloroform or acetonitrile at room temperature. Other precursors using metals such as tin, silicon, selenium and germanium have been reported. Acid hydrolysis with 47% HBr provides a relatively high yield (10-12%) of 6-18F-L-fluorodopa. Luxen et al. [3] compared other available methods for the synthesis of 6-[18F] fluoro-L-3, 4-dihydroxyphenylalanine (6-FDOPA) that are based on labelling by non-regioselective electrophilic fluorination, regioselective fluorodemetallation or nucleophilic substitution. Substitution at position 6 is most desirable, because this does not alter the behavior of dopa, whereas substitutions at 2 and 5 do. It is sterilized by filtering through a 0.22 mm membrane filter, and is supplied at pH between 4.0 and 5.0. Normally EDTA and ascorbic acid are added to the final preparation for stability. The molecular structure of 6-18F-L-fluorodopa is shown in Figure 2.

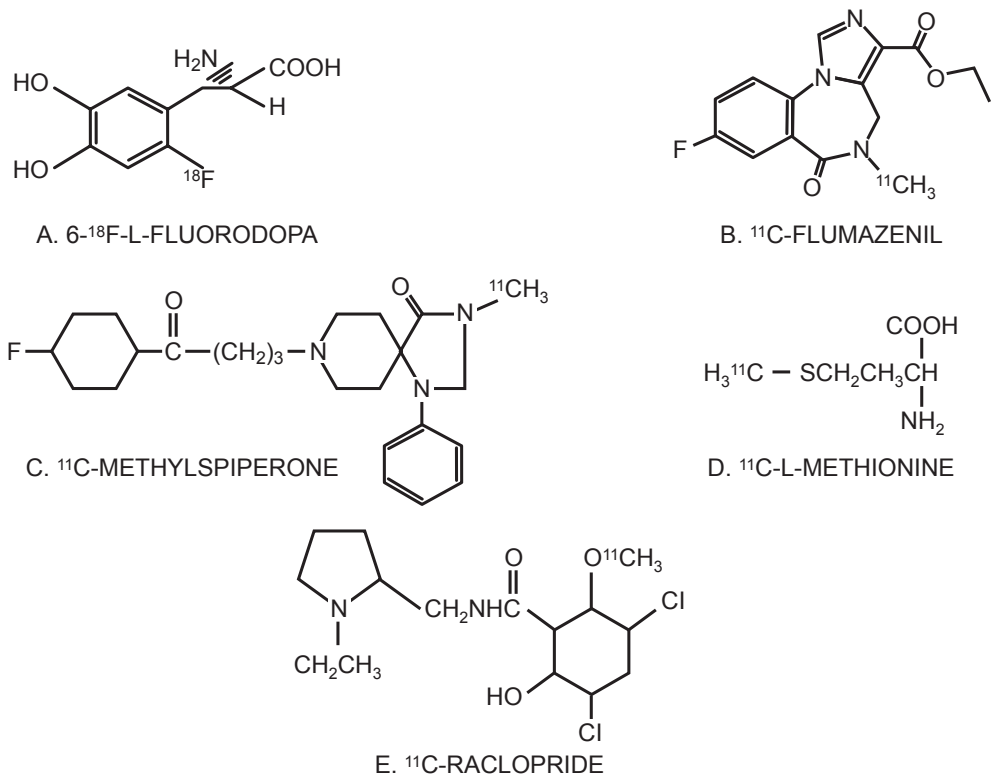

Figure 2. Molecular structure of 6-18F-L-fluorodopa.

Clinical considerations

PET imaging is widely used for the detection of a variety of tumors such as breast, colorectal, esophageal, head and neck, lung, thyroid, melanoma, lymphoma, and other cancers, because of its high sensitivity, specificity, and accuracy. In the interpretation of tumor FDG-PET images, it is desirable to compare the relative tumor FDG uptake with the adjacent normal tissue uptake. Such a comparison offers information on the degree of tumor progression and provides clues to appropriate management of the tumor. In radiation therapy or chemotherapy, comparative evaluation of tumor FDG-PET images before and after therapy is even more useful to assess the effect of therapy on tumor. In all cases the reconstructed images are used to determine the tumor uptake of FDG relative to the normal tissue uptake.

There are several methods (visual, quantitative, and semi-quantitative) to determine the tumor uptake of FDG. Visual assessment is commonly used in tumor diagnosis and staging, and is based on differences in contrast between tumor and adjacent tissue. This is a simplified method requiring only a single static image at a set time after injection and can be equally applied to assess the therapeutic response of the tumor. In the visual technique, it is important to adjust the image intensities of the tumor and adjacent tissues to the same grey or color scale.

While visual assessment of tumor is widely accepted in many nuclear medicine facilities, the quantitative or even semiquantitative method improves the detection and comparative assessment significantly and therefore is highly desirable. Quantitative methods, also called the kinetic methods, include compartmental analysis and Potlak analysis.

Compartmental analysis is based on the fitting of the time-activity curve to a two-compartmental model, using measured arterial activity (input function) and non-linear regression. The time course of activity in tissue is followed by serial imaging and arterial blood sampling. The metabolic rate of glucose given by this method is expressed in moles/min/ml. Potlak analysis provides similar information requiring fewer data and only the integral of the blood activity for input function. Both methods are too complex and expensive, and therefore are less used for routine clinical application.

In semiquantitative methods, static images are utilized as in visual assessment to determine the tissue activity and compare the relative tumor uptake. One method uses an index, the tumor-to-normal tissue activity ratio (T/N), using data from the normal and tumor regions on the reconstructed images. The ratios are independent of the administered dosage, patient's weight or blood glucose level. The T/N ratio assessment is somewhat similar to visual assessment. The choice of

an appropriate normal reference site, particularly in the abdomen and pelvic area, is critical in this analysis.

The most versatile semiquantitative technique is the standard uptake value (SUV) method that is widely used in nuclear medicine and molecular imaging. This value is also less commonly referred to as the differential uptake ratio (DUR). It is defined by the tissue concentration of activity as determined from the region of interest (ROI) on the PET image, divided by the injected dosage of the tracer, and multiplied by a calibration factor, which is basically the body weight, body surface or body lean mass. Thus, SUV = (CROI/A)×WT, where CROI is the decay corrected radiotracer concentration in mCi/g (Bq/g) of tissue in ROI, A is the injected radiotracer dosage in mCi (Bq), and WT is the patient's body weight. In SUV calculation, a ROI is chosen by he reader on the reconstructed image that is displayed on the computer monitor. The computer then calculates the average count density or maximum count density in the ROI, corrects it for the decay for the uptake period and counting efficiency, estimates the area of ROI from the knowledge of pixel size and the number of pixels in ROI, and finally converts the corrected count density to activity per gram of tissue (assuming tissue density is equal to 1 g/cc). From the knowledge of the body weight of the patient and the injected dosage in mCi (Bq), SUV is calculated for the ROI using Eq. (E.1). The FDG SUV values are unitless numbers, and for some normal tissues are: <1 for soft tissues; 1.5-2.0 for blood pool 1 h after injection; ~2.5 for liver and ~3.5 for renal cortex. The SUV values for various neoplastic tissues range from 2 to as high as 25, depending on the avidity of the different cancer cells for FDG. Note that if all of the tracer were uniformly distributed throughout the body, the SUV in each region would be 1. This implies that SUV serves as a normalized T/N ratio index.

It is important to note that the SUV values are affected by several factors. The time period between tracer injection and scanning (i.e., the uptake period) is perhaps the largest single source of error in determining SUV. The time to reach maximum uptake in a given tissue varies with the type and condition of the tissue i.e., different forms of neoplasms and also with tissues before and after therapy. Tissue uptake of FDG decreases with increasing blood glucose level, which affects SUV. Excess body fat falsely elevates SUV, which many investigators correct by using body lean mass instead of body weight. Also, many investigators found better values of SUV using body surface area in place of body weight. The use of maximum pixel count density vs. the average value for all pixels in an ROI also affects SUV values, although the average value now is less commonly used. Thus, SUVs reported in literature are not exactly comparable unless all these parameters are specified.

Technical considerations for combined PET/Diagnostic CT

CT-based attenuation correction

CT-based attenuation correction is subject to error because it requires conversion of the X-ray attenuation factors obtained at diagnostic CT energy (120-140 kVp) to attenuation at PET energy (511 keV). The problem is further complicated by the fact that the spatial distribution of high-density oral and i.v. contrast agents can be quite different during the CT and PET acquisitions. The presence of high density contrast material can result in overestimation of the attenuation factors and falsely increase activity on the PET images [12].

Similar overcorrection artefacts are caused by pacemakers or metallic implants. These artefacts can be clinically insignificant [13]. If not, they can be suppressed with multiphase i.v. injection techniques (contrast agent followed by saline flush) to reduce the effects of high contrast density [14]. The use of negative oral contrast agents, such as water and dilute barium preparation, can also reduce these effects. The extent to which contrast material causes artifacts on PET/CT and thus necessitates use of dual-phase i.v. injection or low-density gastrointestinal contrast material is highly dependent on the scanner and the associated CT attenuation correction software.

Software techniques have been developed to reduce the error attributable to CT attenuation correction. For example, one premise is that iodinated contrast agents have higher density than any physiologically encountered material. The attenuation-correction factor can then be restricted to avoid overcorrection at high radiodensity [15]. Wong et al. [16] found that when these newer attenuation-correction algorithms are applied, oral and i.v. contrast agents no longer cause significant artefacts on PET images. Other authors [17, 18] have found that contrast materials do not cause significant artefacts when newer CT attenuation-correction techniques are used.

Image registration between PET and CT

PET images are acquired over several minutes per table position with the patient quietly breathing. To minimize motion artefacts, CT scans should be obtained with the patient in suspended respiration. The best image registration between CT and PET images

is obtained when the patient suspends respiration at end-tidal volume (quiet end-expiration), because the diaphragm spends the most time in this position during quiet respiration. To obtain well-registered PET/CT images, it is important that patients fully understand the breathing instructions. Many patients have undergone previous CT and need to unlearn the conventional CT instructions for full inspiration. The patient must instead be instructed carefully on breath-holding in quiet end-expiration. Wong et al. [16] have found it very important for the technologist to rehearse the instructions to be given at the time of the scan while observing the patient's breathing to confirm that the patient understands and performs the appropriate breath-hold. Scanning proceeds only after the patient has successfully practiced the breathing maneuver.

Accurate alignment of the PET and CT images requires that the patient remain still throughout the study. Comfort is important, and the patient is held securely on the scanning table with blankets and hook-and-loop (Velcro) straps. The patient is then positioned on the scanner with both arms up. An acrylic board with a set of handles on the scanner table above the patient's head is used to help the patient comfortably maintain the arms-up position and eliminate motion during PET and CT. This device (Wing Board, model MTWB01, Medtec) is the one used routinely for patients undergoing radiation therapy. For all PET/CT examinations, the CT scan is obtained first in the craniocaudal direction. As soon as CT is complete, PET proceeds in the opposite direction beginning at the proximal part of the thighs. This technique minimizes misregistration in the pelvic organs due to normal peristalsis and bladder filling. For head and neck cancer patients, a second PET/CT acquisition is performed with the arms down to image the neck region. In each case, keeping the arms out of the field of view is essential to maintain high quality of the CT images and to reduce truncation artifacts at the edge of the CT field of view.

Image quality of end-expiration chest CT

Diagnostic chest CT scans are usually obtained as part of PET/CT studies. Because these studies are obtained in quiet end-expiratory phase rather than full inspiration, the chest images from PET/diagnostic CT studies show lower lung volumes. More dependent atelectasis and ground-glass opacity typically are seen as a background on these images than on CT scans obtained at full inspiration. It is possible that small nodules are obscured by crowding of vascular structures, and comparison with previous chest CT scans can be difficult. Even after accounting for these factors, Wong et al. [16] found that chest CT images obtained at end-tidal volume are adequate in the patient population referred for oncologic evaluation and undergoing concurrent PET. They have not found it necessary to perform follow-up full-inspiration CT after PET/CT.

In a study of 66 patients with known malignant solid tumors undergoing combined PET/CT, Juergens et al. [19] found that acquisition of an additional low-dose chest CT scan at full inspiration significantly improved sensitivity for detection of small pulmonary nodules. Therefore, the indications and potential value of additional inspiratory chest CT warrant further investigation.

CT tube current modulation

Diagnostic CT exposes patients to a significantly higher radiation dose than do ^{68}Ge transmission CT and low-dose CT (5 mAs) used for attenuation correction. Because the CT scan for PET/CT must be obtained in a single acquisition, optimization of CT parameters for the thoracic and abdominopelvic scans is difficult. At their institution, Wong et al. [16] typically use tube currents of 240 mA (effective tube current, 120 mAs) for chest CT and 340 mA (effective tube current, 170 mAs) for abdominopelvic CT. To maintain high image quality in the abdomen and pelvis while reducing dose to the chest and neck, automated CT tube current modulation is important. Techniques for automated CT tube current modulation vary among scanner manufacturers and have been summarized by Kalra et al. [20]. In some institutions' scanners, automated CT tube current modulation is implemented with the AutomA feature (GE Healthcare). With this feature, the tube current is adjusted in the *z*-direction according to the anteroposterior and lateral scout images obtained during the scan to maintain a specified noise factor [21].

Conclusions

The high precision of PET-CT in the detection of any site in human body that harbors malignant cells makes it an important tool in physicians' hands for both diagnosis of the primary tumor and for restaging and detection of any vital region after completion of radical treatment. With the increasing use of PET-CT in daily clinical practice, this paper is believed to provide all necessary knowledge for a better understanding of its use.

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