Value of PET/CT in Initial Staging and Subsequent Treatment Strategy for Metastatic Breast Cancer

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Data courtesy of University of Tennessee Medical Center, Knoxville, TN, USA

History
A 53-year-old female presented with complaint of back pain. X-rays revealed incidental findings of left breast mass. Patient had a history of smoking and no family history of breast cancer. Mammography revealed a 4 cm x 3.5 cm mass in the left breast and enlarged axillary nodes. Fine needle aspiration cytology (FNAC) of the breast mass showed poorly differentiated infiltrating ductal carcinoma. The patient was referred for PET/CT imaging for initial treatment strategy.

Diagnosis
The PET/CT exam for initial treatment strategy revealed hypermetabolic foci in the left breast that were consistent with known malignancy. In addition, multiple intense hyper-metabolic foci in the left axilla were compatible with metastatic lymph-adenopathy and multiple hyper-metabolic foci involving the bony skeleton were suspicious for osseous metastases (see Figure 1). The patient opted for breast conservation and was given hormonal treatment only.

Approximately 3 years later, the patient fractured her tibia. CT imaging revealed bone metastases of the chest, abdomen and pelvis. A PET/CT was performed (see Figure 2) and this scan was compared to the initial scan with findings consistent of metastatic dis-
ease. The PET/CT used for subsequent treatment strategy revealed a worsening mesenteric and peripancreatic adenopathy along with progression of bony metastases. Suspicion for primary colon neoplasm was noted versus metastatic disease. Colonoscopy was recommended for further evaluation. Supraclavicular and mediastinal lymph nodal metastatic adenopathy was unchanged. In view of the progressive metastatic disease, palliative radiotherapy was advised with a focus on reducing bone pain.

Examination Protocol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan dose</td>
<td>10.1 mCi $^{18}$F FDG $^*$</td>
</tr>
<tr>
<td>Uptake time</td>
<td>90 minutes</td>
</tr>
<tr>
<td>Parameters</td>
<td>6 beds/2 min per bed</td>
</tr>
<tr>
<td>Acquisition</td>
<td>400x400 matrix ultraHD•PET reconstruction</td>
</tr>
<tr>
<td>PET</td>
<td>3 iterations/8 subsets, 5 filter</td>
</tr>
<tr>
<td>CT</td>
<td>120 kV, 250 mAs with Care Dose4D™ 1.5 pitch</td>
</tr>
</tbody>
</table>

$^*$ The full prescribing information for the Fludeoxyglucose F 18 Injection can be found on pages 3-5.

Comments

PET/CT plays an important role in the initial staging as well as in the follow-up of breast carcinoma. In this case, the initial PET/CT study identified tracer avid metastases in the axilla as well as the distal skeleton, which put the patient into an advanced stage. A therapeutic approach including mastectomy with axillary nodal clearance, chemotherapy and radiotherapy as well as hormone replacement therapy based on ER/PR status is an approach in patients in advanced stage breast cancer.

Fludeoxyglucose F18 5-10mCi as an IV injection

Indications and Usage

Fludeoxyglucose F 18 Injection ($^{18}$F FDG) is indicated for positron emission tomography (PET) imaging in the following settings:

- **Oncology:** For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

Important Safety Information

- **Radiation Risks:** Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker.

- **Blood Glucose Abnormalities:** In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.

- **Adverse Reactions:** Hypersensitivity reactions with pruritus, edema and rash have been reported; have emergency resuscitation equipment and personnel immediately available.

Full prescribing information for Fludeoxyglucose F 18 Injection can be found on pages 3-5.

Fludeoxyglucose F 18 injection is manufactured by Siemens’ PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732
The recommended dose:
- for adults is 5 to 10 mCi (185 to 370 MBq), in all indicated clinical settings (2.1)
- for pediatric patients is 2.6 mCi in the neurology setting (2.2).

Start imaging within 40 minutes following drug injection; acquire static emission images 30 to 100 minutes from time of injection (2).

DOSAGE FORMS AND STRENGTHS
Multi-dose vials and single glass vials containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/v ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous injection (3).

ADVERSE REACTIONS
Hypersensitivity reactions have occurred, have emergency resuscitation equipment and personnel immediately available (6).

To report SUSPECTED ADVERSE REACTIONS, contact PETNET Solutions, Inc. at 877-473-8638 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS
Pregnancy Category C: No human or animal data. Consider alternative diagnostics; use only if clearly needed (8.1).

Nursing Mothers: Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding (8.3).

Pediatric Use: Safety and effectiveness in pediatric patients have not been established in the oncology and cardiology setting (8.4).

Radiation dose: Use smallest dose necessary for imaging (5.2).

Blood glucose abnormalities: may cause suboptimal imaging (5.2).

Screen for clinically significant blood glucose abnormalities by obtaining a history and laboratory tests prior to drug injection (5.1).

Encourage the patient to void as soon as the imaging study is completed and as often as possible thereafter for at least one hour (5.2).

To minimize the radiation absorbed dose to the bladder, encourage adequate hydration (5.7).

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Screen for blood glucose abnormalities. In the oncology and neurology settings, instruct patient to fast for 4 to 6 hours prior to the drug’s injection. In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 100 grams) prior to Fludeoxyglucose F 18 Injection facilitates localization of cardiac ischemia (2.3).

Hypothesizes were used to calculate the radiation absorbed dose. Assumptions on the biodistribution shown in Table 1. These estimates were calculated based on human data and the data published by the International Commission on Radiological Protection for Fludeoxyglucose F 18 F. The dosimetry data show that there are slight variations in absorbed radiation dose for various organs in each of the age groups. These dissimilarities in absorbed radiation dose are due to developmental age variations (e.g., organ size, location, and overall metabolic rate for each age group). The identified critical organs (in descending order) across all age groups evaluated are the urinary bladder, heart, pancreas, spleen, and lungs.

Table 1. Estimated Absorbed Radiation Doses (rem/MCi) After Intravenous Administration of Fludeoxyglucose F 18 Injection*

<table>
<thead>
<tr>
<th>Organ</th>
<th>Newborn</th>
<th>1-year old</th>
<th>5-year old</th>
<th>10-year old</th>
<th>15-year old</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(3.4 kg)</td>
<td>(9.8 kg)</td>
<td>(19 kg)</td>
<td>(32 kg)</td>
<td>(57 kg)</td>
<td>(70 kg)</td>
</tr>
<tr>
<td>Bladder wall</td>
<td>4.3</td>
<td>1.7</td>
<td>0.93</td>
<td>0.60</td>
<td>0.40</td>
<td>0.32</td>
</tr>
<tr>
<td>Heart wall</td>
<td>2.4</td>
<td>1.2</td>
<td>0.70</td>
<td>0.44</td>
<td>0.29</td>
<td>0.22</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.2</td>
<td>0.68</td>
<td>0.33</td>
<td>0.25</td>
<td>0.13</td>
<td>0.09</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.2</td>
<td>0.84</td>
<td>0.46</td>
<td>0.29</td>
<td>0.19</td>
<td>0.14</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.96</td>
<td>0.38</td>
<td>0.20</td>
<td>0.13</td>
<td>0.092</td>
<td>0.064</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.81</td>
<td>0.30</td>
<td>0.19</td>
<td>0.13</td>
<td>0.089</td>
<td>0.074</td>
</tr>
<tr>
<td>Airways</td>
<td>0.80</td>
<td>0.8</td>
<td>0.19</td>
<td>0.11</td>
<td>0.058</td>
<td>0.053</td>
</tr>
<tr>
<td>Urethra</td>
<td>0.79</td>
<td>0.35</td>
<td>0.19</td>
<td>0.12</td>
<td>0.076</td>
<td>0.062</td>
</tr>
<tr>
<td>LLI wall</td>
<td>0.69</td>
<td>0.28</td>
<td>0.15</td>
<td>0.097</td>
<td>0.060</td>
<td>0.051</td>
</tr>
<tr>
<td>Liver</td>
<td>0.69</td>
<td>0.31</td>
<td>0.17</td>
<td>0.11</td>
<td>0.076</td>
<td>0.058</td>
</tr>
<tr>
<td>Gallbladder wall</td>
<td>0.69</td>
<td>0.26</td>
<td>0.14</td>
<td>0.093</td>
<td>0.059</td>
<td>0.049</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.68</td>
<td>0.29</td>
<td>0.15</td>
<td>0.096</td>
<td>0.060</td>
<td>0.047</td>
</tr>
<tr>
<td>LLI wall **</td>
<td>0.67</td>
<td>0.27</td>
<td>0.15</td>
<td>0.090</td>
<td>0.057</td>
<td>0.046</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>0.65</td>
<td>0.27</td>
<td>0.14</td>
<td>0.089</td>
<td>0.057</td>
<td>0.047</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.65</td>
<td>0.28</td>
<td>0.15</td>
<td>0.095</td>
<td>0.061</td>
<td>0.048</td>
</tr>
<tr>
<td>Testes</td>
<td>0.64</td>
<td>0.27</td>
<td>0.14</td>
<td>0.085</td>
<td>0.052</td>
<td>0.041</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.62</td>
<td>0.26</td>
<td>0.14</td>
<td>0.089</td>
<td>0.057</td>
<td>0.047</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.61</td>
<td>0.26</td>
<td>0.14</td>
<td>0.086</td>
<td>0.056</td>
<td>0.044</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.61</td>
<td>0.26</td>
<td>0.13</td>
<td>0.080</td>
<td>0.049</td>
<td>0.039</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.58</td>
<td>0.25</td>
<td>0.13</td>
<td>0.078</td>
<td>0.049</td>
<td>0.039</td>
</tr>
<tr>
<td>Bone surface</td>
<td>0.57</td>
<td>0.24</td>
<td>0.12</td>
<td>0.079</td>
<td>0.052</td>
<td>0.041</td>
</tr>
<tr>
<td>Breast</td>
<td>0.54</td>
<td>0.22</td>
<td>0.11</td>
<td>0.068</td>
<td>0.043</td>
<td>0.034</td>
</tr>
<tr>
<td>Skin</td>
<td>0.49</td>
<td>0.20</td>
<td>0.10</td>
<td>0.060</td>
<td>0.037</td>
<td>0.030</td>
</tr>
<tr>
<td>Brain</td>
<td>0.29</td>
<td>0.13</td>
<td>0.09</td>
<td>0.078</td>
<td>0.072</td>
<td>0.070</td>
</tr>
<tr>
<td>Other tissues</td>
<td>0.59</td>
<td>0.25</td>
<td>0.13</td>
<td>0.083</td>
<td>0.052</td>
<td>0.042</td>
</tr>
</tbody>
</table>

MIRDose 2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution based on data from Galagher et al. and Jones et al.

The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used. *LLI = lower large intestine; **LLI = upper large intestine.
2.5 Radiation Safety – Drug Handling
• Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling Fludeoxyglucose F 18 Injection to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel and other persons.
• Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
• Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient (see Description (11.2)).
• The dose of Fludeoxyglucose F 18 used in a given patient should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.

2.6 Drug Preparation and Administration
• Calculate the necessary volume to administer based on calibration time and dose.
• Aseptically withdraw Fludeoxyglucose F 18 Injection from its container.
• Inspect Fludeoxyglucose F 18 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
• Do not administer the drug if it contains particulate matter or discoloration; dispose of these unacceptable or unused preparations in a manner consistent with applicable regulations.
• Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS.

2.7 Imaging Guidelines
• Initiate imaging within 40 minutes following Fludeoxyglucose F 18 Injection administration.
• Acquire static emission images 30 to 100 minutes from the time of injection.

3 DOSAGE FORMS AND STRENGTHS
Multiple-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) of Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/v ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Radiation Risks
Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker (see Dosage and Administration (2.5)).

5.2 Blood Glucose Abnormalities
In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.

6 ADVERSE REACTIONS
Hypersensitivity reactions with pruritus, edema and rash have been reported in the post-marketing setting. Have emergency resuscitation equipment and personnel immediately available.

7 DRUG INTERACTIONS
The possibility of interactions of Fludeoxyglucose F 18 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
• Pregnancy Category C

Animal reproduction studies have not been conducted with Fludeoxyglucose F 18 Injection. It is also not known whether Fludeoxyglucose F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Consider alternative diagnostic tests in a pregnant woman; administer Fludeoxyglucose F 18 Injection only if clearly needed.

8.3 Nursing Mothers
It is not known whether Fludeoxyglucose F 18 Injection is excreted in human milk. Consider alternative diagnostic tests in nursing women who are breast-feeding.

8.4 Pediatric Use
The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatric patients with epilepsy, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight has not been determined. In the oncology and radiology settings, the safety and effectiveness of Fludeoxyglucose F 18 Injection have not been established in pediatric patients.

11 DESCRIPTION
11.1 Chemical Characteristics
Fludeoxyglucose F 18 Injection is a positron-emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[18F]fluoro-D-glucose has the molecular formula of C12H22FNO6 with a molecular weight of 220.26, and has the following chemical structure:

\[ \text{C}_{12}\text{H}_{22}\text{FNO}_6 \]

Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.740 to 7.4048 mCi (20.0 to 200 mCi) of 2-deoxy-2-[18F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/v ethanol as a stabilizer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

11.2 Physical Characteristics
Fluorine F 18 decays by emitting positron to Oxygen O 16 (stable) and has a physical half-life of 109.7 minutes. The principal photons useful for imaging are the dual 511 keV gamma photons, that are produced and emitted in opposite direction when the positron interacts with an electron (Table 2).

Table 2. Principal Radiation Emission Data for Fluorine F 18

<table>
<thead>
<tr>
<th>Radiation/Emission</th>
<th>% Per Disintegration</th>
<th>Mean Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positon (β+)</td>
<td>96.73</td>
<td>249.8 keV</td>
</tr>
<tr>
<td>Gamma (γ) (≈)</td>
<td>3.27</td>
<td>511.0 keV</td>
</tr>
</tbody>
</table>

*Produced by positron annihilation.

From: Kocher, D.C. Radioactive Decay Tables DOE/TO-11026, 89 (1981)

The specific gamma ray constant (joint source air kerma coefficient) for fluorine F 18 is 5.7 Rhm/1 (3.35 x 10-6 GY/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4 mm lead (Pb). The range of attenuation coefficients for this radionuclide is shown in Table 3. For example, the interposition of an 8 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

Table 3. Radiation Attenuation of 511 keV Photons by lead (Pb) shielding

<table>
<thead>
<tr>
<th>Shield thickness (Pb) mm</th>
<th>Coefficient of attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>0.909</td>
</tr>
<tr>
<td>6</td>
<td>0.826</td>
</tr>
<tr>
<td>8</td>
<td>0.683</td>
</tr>
<tr>
<td>10</td>
<td>0.500</td>
</tr>
<tr>
<td>11</td>
<td>0.398</td>
</tr>
<tr>
<td>20</td>
<td>0.250</td>
</tr>
</tbody>
</table>

*Calibration time.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Fludeoxyglucose F 18 is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose F 18 is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [18F]FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of Fludeoxyglucose F 18 reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and Fludeoxyglucose F 18 transport and phosphorylation (expressed as the ‘lumped constant’ ratio), Fludeoxyglucose F 18 is used to assess glucose metabolism.

In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of Fludeoxyglucose F 18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of Fludeoxyglucose F 18 reflect greater than normal rates of glucose metabolism.

12.2 Pharmacodynamics
Fludeoxyglucose F 18 Injection is rapidly distributed to all organs of the body after intravenous administration. After background clearance of Fludeoxyglucose F 18 Injection, optimal PET imaging is generally achieved between 30 to 40 minutes after administration.

In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (1) an increase in activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by Fludeoxyglucose F 18 accumulation shows considerable variability. Depending on tumor type, stage, and location, Fludeoxyglucose F 18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of Fludeoxyglucose F 18.

In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial substrate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these condi-
ions, phosphorylated Fludeoxyglucose F 18 accumulates in the myocyte and can be detected with PET imaging. In the brain, cells normally rely on aerobic metabolism. In epilepsy, the glucose metabolism varies. Generally, during a seizure, glucose metabolism increases. Interictally, the seizure focus tends to be hypometabolic.

12.9 Pharmacokinetics

Distribution: In four healthy male volunteers, receiving an intravenous administration of 30 seconds in duration, the arterial blood level profile for Fludeoxyglucose F 18 decayed triexponentially. The effective half-life ranges of the three phases were 0.2 to 0.3 minutes, 10 to 13 minutes with a mean and standard deviation (STD) of 11.6 ± 1.1 min, and 80 to 95 minutes with a mean and STD of 88 (±) 4 min. Plasma protein binding of Fludeoxyglucose F 18 has not been studied.

Metabolism: Fludeoxyglucose F 18 is transported into cells and phosphorylated to (\*F)FDG-6-phosphate. The FDG-6-phosphate is at a rate proportional to the rate of glucose utilization within that tissue. The PET and fluorodeoxyglucose (FDG) metabolic images are normally examined together.

Fludeoxyglucose F 18 injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-glucose (CDGC), 2-deoxy-2-phospho-D-glucose (CDGP), 2-deoxy-2-chloro-6-phospho-D-mannose (CDPM-6-phosphate)). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDP, CDG, and CDM) presumably leave cells by passive diffusion. Fludeoxyglucose F 18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Clearance from the cardiac tissue may require more than 96 hours. Fludeoxyglucose F 18 is not involved in glucose metabolism in any tissue is then excreted in the urine. Elimination: Fludeoxyglucose F 18 is cleared from most tissues within 24 hours and can be eliminated from the body unchanged in the urine. Three elimination phases have been identified in the reviewed literature. Within 33 minutes, a mean of 3.9% of the administered radioactive dose was measured in the urine. The amount of radiation exposure of the urinary bladder at two hours post-administration suggests that 20.6% (mean) of the radioactive dose was present in the bladder.

Special Populations

The pharmacokinetics of Fludeoxyglucose F 18 Injection have not been studied in elderly patients, hepatically impaired or pediatric patients. Fludeoxyglucose F 18 is eliminated through the renal system. Avoid excessive radiation exposure to this organ system and adjacent tissues. The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on Fludeoxyglucose F 18 distribution in humans have not been ascertained (see Warnings and Precautions (5.1)).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the Fludeoxyglucose F 18 Injection carcinogenic potential, mutagenic potential or effects on fertility.

14 CLINICAL STUDIES

14.1 Oncology

The efficacy of Fludeoxyglucose F 18 Injection in positron emission tomography (PET) imaging was demonstrated in 16 independent studies. These studies prospectively evaluated the use of Fludeoxyglucose F 18 in patients with suspected or known malignancies, including non-small cell lung cancer, colorectal, pancreatic, breast, thyroid, melanoma, Hodgkin's and non-Hodgkin's lymphoma, and various types of metastatic cancers to lung, liver, bone, and axillary nodes. All these studies had at least 50 patients and used pathology as a standard of truth. The Fluodeoxyglucose F 18 Injection doses in the studies ranged from 200 MBq to 740 MBq with a median and mean dose of 370 MBq. In the studies, the diagnostic performance of Fludeoxyglucose F 18 Injection varied with the type of cancer, size of cancer, and other clinical conditions. False negative and false positive scans were observed. Negative Fludeoxyglucose F 18 Injection PET scans do not exclude the diagnosis of cancer. Positive Fludeoxyglucose F 18 Injection PET scans can not replace pathology to establish a diagnosis of cancer. Non-malignant conditions such as fungal infections, inflammatory processes and benign tumors have patterns of increased glucose metabolism that may give rise to false positive scans. The efficacy of Fluodeoxyglucose F 18 Injection PET imaging in cancer screening was not studied.

14.2 Cardiology

The efficacy of Fludeoxyglucose F 18 Injection for cardiac use was demonstrated in ten independent, prospective studies of patients with coronary artery disease and chronic left ventricular systolic dysfunction who were scheduled to undergo coronary revascularization. Before revascularization, patients underwent PET imaging with Fluodeoxyglucose F 18 Injection (74 to 370 MBq, 2 to 10 mCi) and perfusion imaging with other diagnostic radio-pharmaceuticals. Doses of Fludeoxyglucose F 18 Injection ranged from 74 to 370 MBq (2 to 10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared in a blinded manner to assessments made after successful revascularization to identify myocardial segments with functional recovery. Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed Fluodeoxyglucose F 18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed reductions in both Fludeoxyglucose F 18 accumulation and perfusion (i.e., match defects).

Findings of flow-metabolism mismatch in a myocardial segment may suggest that successful revascularization will restore myocardial function in that segment. However, false positive scans occur relatively rarely, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment may suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted with Fludeoxyglucose F 18 PET imaging depends on successful coronary revascularization. Therefore, in patients with a low likelihood of successful revascularization, the diagnostic usefulness of PET imaging with Fludeoxyglucose F 18 Injection is more limited.

14.3 Neurology

In a prospective, open label trial, Fludeoxyglucose F 18 Injection was evaluated in 86 patients with epilepsy. Each patient received a dose of Fludeoxyglucose F 18 Injection in the range of 185 to 370 MBq (6 to 10 mCi). The mean age was 16.4 years (range: 4 months to 58 years; of these, 42 patients were less than 12 years and 16 patients were less than 2 years old). Patients had a known diagnosis of complex partial epilepsy and were under evaluation for surgical treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEGs and sphenoidal EEGs. Fludeoxyglucose F 18 Injection PET imaging confirmed previous diagnostic findings in 16% (1487 of the patient's in 34% (1087) of the patients, Fludeoxyglucose F 18 Injection PET images provided new findings. In 32% (2787), imaging with Fludeoxyglucose F 18 Injection was inconclusive. The impact of these imaging findings on clinical outcomes is not known. Several other studies comparing imaging with Fludeoxyglucose F 18 Injection results to subphenoidal EEG, MR and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci. The safety and effectiveness of Fludeoxyglucose F 18 Injection to distinguish idiopathic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

REFERENCES


15 HOW SUPPLIED/STORAGE AND DRUG HANDLING

Fludeoxyglucose F 18 Injection is supplied in a multi-dose, capped 30 mL and 50 mL glass vial containing between 0.746 to 2.40 GBq/mL (20 to 200 mCi/mL). of non carrier-added 2-deoxy-2-[F-18] fluoro-D-glucose, at end of synthesis, in approximately 15 to 50 mL. The contents of each vial are sterile, pyrogen-free and preservative-free.

NDC 40028-511-30, 40028-511-50

Receipt, transfer, handling, possession, or use of this product is subject to the radiative material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

Store the Fludeoxyglucose F 18 Injection vial upright in a lead shielded container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store and dispose of Fludeoxyglucose F 18 Injection in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State. The expiration date and time are provided on the container label. Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS time.

17 PATIENT COUNSELING INFORMATION

Instruct patients in procedures that increase renal clearance of radioactivity. Encourage patients to:

- drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.

Manufactured by: PETNET Solutions Inc. 810 Innovation Drive Knoxville, TN 37922

Distributed by: PETNET Solutions Inc. 810 Innovation Drive Knoxville, TN 37922

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