Effective use of a new quality and safety checklist for the steady and safe supply of fluorine-18 fluorodeoxyglucose for positron emission tomography/computed tomography

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Keywords: Checklist
- ^{18}F-FDG PET
- Quality control test
- Radiation exposure

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Received:
18 May 2012
Accepted revised:
25 June 2012

Abstract

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) with the in-hospital synthesis of ^{18}F-FDG was initiated in our hospital on April 1, 2010. *We aim* to perform stable supply of ^{18}F-FDG for patients and to avoid unnecessary radiation exposure due to mis-preparation of ^{18}F-FDG. Pharmacists perform quality control tests to determine whether ^{18}F-FDG meets official regulations. After the quality control test, we give ^{18}F-FDG that conforms to these standards to patients to conduct ^{18}F-FDG PET/CT. After a quality control test is initiated, various problems can occur including leakage and staff radiation exposure. *We recorded* daily radiation exposure in the hot lab and calculated the average daily radiation exposure on a monthly basis for a period of one year. We developed a checklist to safely and quickly synthesize^{18}F-FDG for patients. *The total radiation exposure* of the three pharmacists was 394, 180, and 214μSv/y and overall lower than the occupational maximum values (≤50mSv/year and ≤100mSv/5years for males). *In conclusion*, using the new checklist, pharmacists and the operator of the Sumitomo Heavy Industries Accelerator service Co., Ltd. were able to practice their daily work effectively during the synthesis and quality control testing of ^{18}F-FDG. Notably the usual radiation exposure reported in the present study was quite lower than the allowable maximum.

Hell J Nucl Med 2012; 15(2): 130-133 *Published on line: 27 July 2012*

Introduction

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is currently one of the most useful diagnostic modalities especially for detecting and diagnosing cancer but also for other clinical applications. The synthesizer of ^{18}F-FDG was approved as medical equipment in December 2001; it can synthesize ^{18}F-FDG within hospitals for use in patients. Fluorine-18-FDG PET/CT was approved as a health care service provided by national health insurance in April 2002. It was approved by the Ministry of Health, Labour, and Welfare in September 2005 as a medicine available under health insurance and has been supplied to hospitals since then. In our hospital, ^{18}F-FDG PET/CT was initiated on April 1, 2010. As we are unable to have ^{18}F-FDG delivered since we are out of the service range due to the short half-life of ^{18}F-FDG, we synthesize ^{18}F-FDG and perform quality control tests within the hospital. The quality control requirements of ^{18}F-FDG are outlined in the United States Pharmacopeia 25th edition, British Pharmacopeia 2000, and European Pharmacopeia 4th edition [1]. However, as it is not mentioned in the Japanese Pharmacopeia 16th edition, we perform quality control testing for ^{18}F-FDG according to the guidelines in our hospital that were created on the basis of the guidelines of the Japanese Society of Nuclear Medicine [2]. The test items are listed in Table 1.

Since the time we first used PET/CT in our hospital, the pharmacists and operator cooperated and confirmed each other's work to avoid mis-preparation of ^{18}F-FDG. Problems occurred only during the introduction period. As our hospital treats patients in a broad area including islands, mis-preparation greatly influences treatment. Therefore, we created a method to prevent this mis-preparation Although there are studies on the synthesis and quality control of ^{18}F-FDG, none refers to the risks due to human errors in the daily preparation work of ^{18}F-FDG. Therefore, we report such errors in the present study. In addition, we studied the radiation exposure of the pharmacists performing in the synthesis of ^{18}F-FDG in the hot lab.

Supply of ^{18}F-FDG for use in PET/CT

In-hospital synthesis of ^{18}F-FDG

Fluorine-18-FDG, in which a part of D-glucose was replaced by fluorine-18, was used as a PET radiotracer and is prepared by a full-time operator (Sumitomo Heavy Industries (SHI)

Table 1. *Quality control tests of ^{18}F-FDG*

Tests performed before intravenous injection
Visual inspection (clear, colorless, particulate free) Radiochemical purity (>95% HPLC) Radionuclidic identity (0.511MeV) pH (5.0–8.0) Bacterial endotoxins (passes LAL tests; 20min) Kryptofix Color-Spot test (≤40ppm) Al (≤10ppm) Half-life (105-115min)
Retrospective tests
Sterility (passes the 7 days test)

Accelerator Service Co., Ltd., Tokyo, Japan) as described by Hammacher [3].

Participation of pharmacists in the supply of ^{18}F-FDG

Pharmacists confirmed the set-up of the synthesizer (F200, SHI, Ltd., Tokyo, Japan) of ^{18}F-FDG arranged by the operator before synthesis, and performed quality control tests of the synthesized ^{18}F-FDG. We administered ^{18}F-FDG to target patients, only after all tests mentioned in Table 1 were cleared, processed and conformed to the standards. Three pharmacists were in charge and had taken alternate turns every week.

Problems that were encountered during the quality control tests of ^{18}F-FDG

a) Leakage of ^{18}F-FDG due to a connection deficiency in a tube and the needle with which we pricked the top of the withdrawal multi-dose vial (Fig. 1b). b) Improper connection of the tube and the air out-flow releasing the synthesized ^{18}F-FDG for sampling and withdrawal from vials (Fig. 1a). c) Leakage of ^{18}F-FDG due to a connection lapse of tubes sending synthesized ^{18}F-FDG to the quality control testing device (Fig. 1c). d) Leakage of ^{18}F-FDG as a result of forgetting the setting of the sample tube for bacterial endotoxins test.

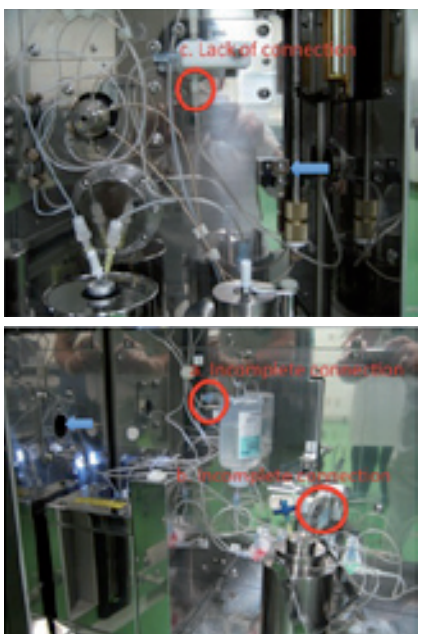

Figure 1. Mis-preparations in the quality control test for synthesized ^{18}F-FDG. Problems encountered at a point herewith by a circle of a, b, c.

Therefore, we needed to develop certain countermeasures in order to avoid several serious errors that can generally occur and to ensure the steady and safe supply of ^{18}F-FDG.

Materials and methods

This study was performed with complete consideration of human rights.

Although after synthesis we performed quality control tests for ^{18}F-FDG in a hot cell (SHI, Ltd., Tokyo, Japan) without radiation exposure, the sterility test had to be performed directly outside the hot cell, i.e. to sample about 0.1mL of the synthesized ^{18}F-FDG solution with radiation exposure.

As there are limitations for radiation exposure, we recorded daily radiation exposure from entrance into the hot lab until exit. We calculated the average daily radiation exposure of the personnel on a monthly basis using dosimeters (ALOKA PDM-112, AS ONE Corporation, Osaka, Japan) placed in the upper-left pocket of the white gowns.

Test syntheses were carried out in March 2010, prior to full-scale operation which started from April 2010 onwards. One pharmacist checked the ^{18}F-FDG synthesizer and performed the quality control test of ^{18}F-FDG in the hot lab, whereas another pharmacist asked as the examiner by using a manual procedure containing a checklist of about 110 items. We repeated these procedures in rotation, several times, after confirming that each one of us alone could perform our respective duties satisfactorily.

The manual procedure used during training was useful but difficult to use during our actual work due to time limitations. As every pharmacist works alone, spending time using a checklist containing approximately 110 items was quite time-consuming. Therefore, we developed a novel abridged quality procedure checklist (Table 2). We depicted the items for which problems have occurred in bold-faced characters to highlight their importance. The operator provided the main items that he wanted to be confirmed mainly by pharmacists (e.g., whether reagents before synthesis were exactly set etc.), and pharmacists provided the items that they wanted to be confirmed mainly by the operator (e.g., whether tubes were set definitely etc.) on an A4 paper-sized checklist. We revised this list to be included within 1 sheet to be shared by the operator and the pharmacists.

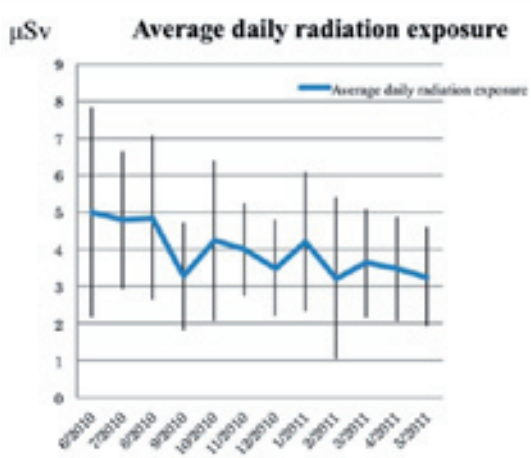

Figure 2. Average daily radiation exposure of pharmacists.

Table 2. *Checklist for the preparation of ^{18}F-FDG*

PET Check List (Niigata Cancer Center Hospital) ver.23.2.18
∗Subjects: Carefully check subjects without pc error sensor.
∗Bold items: Items in which problems occurred previously; **items to pay attention to**.
∗Markbox with check ☑

Date

<Quality control test>
☐ Prepare the reagent for bacterial endotoxins (remove from refrigerator)
☐ Check the size of vials and dirt (30mL:2 vials, 20mL:1vial, 3mL:1 vial)
☐ Prepare the reagent for sterility for the next day (keep in incubator)

Checker Pharmacist

<Synthesizer>
☐ 1.Confirm 5 reagents for synthesis (colors of tubes and reagent vials, centesis to vial bottoms)
☐ 2.Confirm the vial for synthesis (no inclination of the vial)
☐ 3.Confirm filters (from the top small:IC-H(brown) → medium:PS-2(blue) → large:alumina(green))
☐ 4.Confirm the volume of reused ^{18}O water (left of synthesizer,under the baseline)

<Device to distribute ^{18}F-FDG>
The vial for synthesized ^{18}F-FDG
☐ 1.Confirm line connection to nitrogen gas purge
☐ 2.Confirm product line (no tension in line)
☐ 3.Confirm the needle (22-G X70-mm; centesis to the vial bottom and no inclination of the vial)
☐ 4.Confirm connection points of tubes and screw tightly
(left: vial for synthesized ^{18}F-FDG, red: purge, yellow: water for injection, blue: 10-mL syringe, brown: takeoff vial, green: reserve vial, right: sample vial)

Checker Operator

Takeoff vial
☐ Confirm the takeoff vial (30mL)
☐ Confirm the ventilation needle (22-G X 70-mm +millex filter FG)
☐ **Confirm connection between the needle(19-G X 120-mm) and tube; screw it tightly**

<Device of quality control test>
Test
☐ Confirm connections of theT-shaped stopcock and 3 tubes
(bottom: device to distribute ^{18}F-FDG, left:sample vial, top:endotoxins)
☐ Test papers (pH test paper, Alumi check test paper, TLC test paper)
☐ Confirm ventilation needles (sample vial and waste fluid vial)
☐ Confirm the substitution of the needle (from the waste fluid vial to the sample vial, 20-G X 70-mm)
Toxinometer
☐ Confirm the fixation of the route (fix the tube to ditches, fix the tube's top using the clip)
☐ **Confirm the setting of the falcon tube**
☐ Confirm the position of the chip (indicated by the mark)
☐ Confirm the endotoxin test reagent (set it 15 min after the start of FDG synthesis)

Results

We recorded the daily average radiation exposure of the dosimeters from June 2010 to May 2011 (Fig. 2). The total radiation exposure of the pharmacists was 394, 180, and 214μSv/year, respectively.

Since the implementation of the new daily checklist, no serious problems related to leakage were reported by the operator or the pharmacists from February to December 2011. In addition, the checklist caused no extra time burden because it fitted on a single sheet of A4 paper.

Discussion

The radioactivity doses were small from the outset and further decreased gradually (Fig. 2). In June 2010, the average radiation exposure was 5.0μSv during PET-related work time, but decreased to 3.3μSv in May 2011. The pharmacists became used to the work procedure and were able to perform series of work tasks in a short time. This appears to be the main factor that decreased radiation exposure. The total radiation exposure of each of the three pharmacists (394, 180, and 214μSv/year) was considerably smaller than the occupational maximum values (≤50mSv/year and ≤100mSv/5years for males) permitted according to the Medical Service Law, Laws Concerning the Prevention from Radiation Hazards due to Radioisotopes and Others, and the 2007 recommendations of the International Commission on Radiological Protection. The ^{18}F-FDG synthesizer is more automated than former models. Employees have given care to avoid radiation exposure by using devices such as lead blocks and lead glass [4].

Before using the checklist, in cases of potential for connection-related accidents of the tubes, when a pharmacist prepared the quality control test, these were avoided by checking the indications of the operator several times

before using the checklist. The problems reported in this study included the leaks that occurred even after the double-check by the pharmacist and operator without using the checklist. Consequently, the pharmacists and operator became consciously aware of points preventing problems by using the checklist.

In conclusion, we believe that our quality and safety checklist avoids unnecessary radiation exposure and patient program delays. There are no reports of the potential of mis-preparation of ^{18}F-FDG in the literature. The usual radiation exposure (three pharmacists' average: 263μSv/year) reported in the present study is quite lower than the maximum (≤50mSv/year and ≤100mSv/5years for males) allowed according to current radiation protection regulations. Since unexpected problems may occur, we shall continue improving the stable and safe supply of ^{18}F-FDG for patients.

The authors declare that they have no conflicts of interest.

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