Cellular and Molecular Biology [TM] **55**, N°3, 29-33
DOI 10.1170/T871

ISSN 1165-158X
2009 Cell. Mol. Biol.[TM]

A METHODOLOGY TO EVALUATE OCCUPATIONAL INTERNAL EXPOSURE TO FLUORINE-18

C. M. OLIVEIRA, A. L. A. DANTAS AND B. M. DANTAS*

Instituto de Radioproteção e Dosimetria, Comissão Nacional de Energia Nuclear
Av. Salvador Allende - CEP 22780-160, Rio de Janeiro, RJ, Brasil
* Fax +55 021 2442-2405 *Email : bmdantas@ird.gov.br

Received, September 1st 2008; Accepted October 1st, 2009; Published November 15th, 2009

Abstract – The objective of this work is to develop procedures for internal monitoring of ^{18}F to be applied in cases of possible incorporation of fluoride and ^{18}FDG, using *in vivo* and *in vitro* methods of measurements. The Na I (Tl) 8"x 4" scintillation detector installed at IRD-Whole Body Counter was calibrated for measurements with a whole body anthropomorphic phantom, simulating homogeneous distribution of ^{18}F in the body. The NaI(Tl) 3"x 3" scintillation detector installed at the IRD-Whole Body Counter was calibrated for *in vivo* measurements with a brain phantom inserted in an artificial skull, simulating ^{18}FDG incorporation. The HPGe detection system installed at the IRD-Bioassay Laboratory was calibrated for *in vitro* measurements of urine samples with 1 liter plastic bottles containing a standard liquid source. A methodology for bioassay data interpretation, based on standard ICRP models edited with the software AIDE-version 6, was established. It is concluded that *in vivo* measurements have sufficient sensitivity for monitoring ^{18}F in the forms of fluoride and ^{18}FDG. The use of both *in vitro* and *in vivo* bioassay data can provide useful information for the interpretation of bioassay data in cases of accidental incorporation in order to identify the chemical form of ^{18}F incorporated.

Key words: FDG, Nuclear medicine, internal dosimetry.

INTRODUCTION

^{18}F has a half-life of 109.7 min and decays by positron emission (96.9%) or electronic capture, with abundance of 3.1%, being transformed into stable ^{18}O. The maximum energy of β+ particles is 635 keV (100%), reaching 2.4 mm in water, suffering annihilation when interacting with electrons of the media and resulting in the formation of two 511 keV annihilations photons (193%), in opposite directions, forming an angle of about 180° (3,8).

Production of ^{18}FDG in Brazil

^{18}F is produced basically for the synthesis of the radiopharmaceutical ^{18}FDG, used in about 95% of PET examinations (1). PET technique allows assessing metabolic processes in healthy or pathologic conditions, unlike conventional techniques that assess solely anatomy and morphology of tissues, such as magnetic resonance and computed tomography. When ^{18}FDG is injected in the human body it follows the metabolism of glucose in the cells. After reaching the interior of the cells, ^{18}FDG molecule transforms onto ^{18}FDG-6-phosphate, by the action of hexokinase enzyme, being retained by cells and not being metabolized by phosphorglucose isomerase in the glycolytic way. This enzyme does not recognize the glucose molecule labeled by ^{18}F in the carbon-2 position, because it should find a hydroxyl group in the natural glucose molecule. This retention time is essential for the accomplishment of studies in tissues and organs. Glucose is the main source of energy for all body cells. As a result, ^{18}FDG presents a uniform distribution in the body. However, brain, heart and malignant tumors present accelerated metabolism, demanding higher amounts of glucose. Therefore ^{18}FDG is indicated to evaluate metabolic processes in the areas of neurology, cardiology and oncology (7,9,10)

In Brazil, ^{18}F is produced in São Paulo at Instituto de Pesquisas Energéticas Nucleares, IPEN-CNEN/SP, and in Rio de Janeiro at Instituto de Engenharia Nuclear, IEN – CNEN/RJ. Clinics in São Paulo and Rio de

Abbreviations: AIDE, activity internal dose estimates; **HPGE**, High Performance Germanium; **IRD**, Institute for Radioprotection and Dosimetry; **PET**, positron emission tomography

Janeiro had initiated the process of purchasing new Tomography PET/CT. Therefore the production of ^{18}F at those cities can supply the demand for PET procedures. New facilities in the cities of Recife and Belo Horizonte have recently started ^{18}FDG production aiming to attend the increasing demand for PET examinations in the North and Southwest regions of the country (9).

Occupational exposure to ^{18}F

The identification of critical steps in terms of occupational exposure in the ^{18}FDG production was carried out at the Instituto de Energia Nuclear, IEN-CNEN/RJ. ^{18}F is produced in Particle Accelerators called cyclotrons in the form of ions ($^{18}F^-$) through the irradiation of ^{18}O enriched water by proton beam bombardment. The amount of ^{18}F recovered is usually between 600 and 6000 mCi (22.2 and 222 GBq) (4).

After irradiation, the ions fluorides are transferred to the Synthesis Cell, located at the Hot Chemistry Laboratory, where the glucose molecule is added to the fluorine atom, forming the ^{18}FDG. After the synthesis, ^{18}FDG solution is transferred to the fractionation cell, where the samples are distributed in doses to be delivered to the clinics. The activity of each dose is calibrated and the vials are sealed up and sent to the Laboratory of Quality Control and afterwards to the nuclear medicine clinics. The resulting ^{18}FDG solution (about 17 mL) should be clear, colorless, neutral and isotonic (4). In the quality control step the workers manipulate unsealed sources, using a volume of 0.425 mL (about 2 % of the total final solution of ^{18}FDG), with high specific activity, which represents a risk of incorporation.

The increasing production and clinical use of ^{18}FDG leads to the increase in the number of occupationally exposed workers and the probability of incorporation. Despite of the low risks of incorporation due to safe production conditions, the technicians involved in its production can be exposed to fluoride ions and ^{18}FDG molecule in the case of unusual events, that is, in accidents or incidents situations along the ^{18}F production line, ^{18}FDG synthesis and at the Quality Control Laboratory. Therefore, the objective of this work is to develop procedures for internal monitoring of ^{18}F in the form of fluoride ions and ^{18}FDG, using *in vivo* and *in vitro* bioassay methods of measurements. The development of such methodologies for the evaluation of ^{18}F incorporation provides useful tools for the verification of the workplace safety, assuring workers welfare.

MATERIALS AND METHODS

Standard source

Because of the short half-life of ^{18}F, a standard liquid source of ^{22}Na was used, for the calibration of the i*n vivo* and *in vitro* detection systems. The ^{22}Na was supplied and certified by Laboratório Nacional de Metrologia das Radiações Ionizantes (LNMRI-IRD/CNEN). ^{22}Na has a half-life of 2.6 years, decays by positron emission, suffering annihilation, resulting in the formation of two 511 keV photons. Its longer half-life allows the time necessary for the performance of the calibrations. ^{22}Na activity was converted into ^{18}F equivalent activity, taking into account the ratio between gamma intensity of both radionuclides, ^{18}F and ^{22}Na, through the equation:

$$^{18}F_{Eq} = {}^{22}Na_{Act} x (\gamma\,{}^{22}_{Na} / \gamma\,{}^{18}_{F}) \qquad (1)$$

Where: $^{18}F_{Eq}$ is the Equivalent activity of ^{18}F; $^{22}Na_{Act}$ is the activity of the ^{22}Na standard source; $\gamma\,{}^{22}_{Na}$ and $\gamma\,{}^{18}F$ are the gamma intensities of ^{22}Na and ^{18}F, at 511 keV.

Calibration procedures

In vitro measurement technique was implemented at the IRD-Bioassay Laboratory using a HPGe detection system and consists on the identification and quantification of ^{18}F in urine samples. In order to obtain a calibration curve of efficiency *versus* sample volume, 4.37 ± 0.04 kBq of ^{22}Na standard liquid solution was transferred to a 1L plastic bottle and a series of ten 15-minutes counting was performed, with increasing volumes (from 100 up to 1000 mL) of 1 Molar HNO_3 added sequentially to the bottle.

The calibration factor for each volume is defined by the ratio between the count rate at 511 keV region and the solution activity. The calibration factors are expressed in cpm Bq^{-1}. An additional 15 minutes count of a 1 liter urine sample supplied by a non-exposed individual was performed in order to calculate the MDA (minimum detectable activity) of the *in vitro* technique.

The *in vivo* measurement techniques were standardized at the IRD-Whole Body Counter. For the calibration of the technique aimed to estimate incorporation of fluoride, a whole body anthropomorphic phantom was produced, containing 41.8 ± 0.4 kBq of ^{22}Na standard liquid solution homogeneously distributed in a set of polyethylene containers of different volumes. Such approach was adopted because of the expected homogeneous distribution of ^{18}F within the whole skeleton in the case of incorporation of fluoride ions. The phantom is comprised by 2 containers of 20 L, simulating the chest, 1 bottle of 5 L, simulating the head and 7 bottles of 2 L, simulating arms and legs. The total volume of the phantom is 59 L. This was the best approximation of a human body using plastic bottles that could be accommodated on the monitoring chair.

The ^{22}Na standard solution was added to each bottle in the proportion of 1mL per liter of bottle volume by using a precision micro-pipette. The remaining volume of each bottle was completed with 1 Molar HNO_3 solution. The phantom was positioned as a human being for the measurements with a NaI(Tl) 8"x 4" scintillation detector installed in the shielded room of the whole body counter, as shown in Figure 1. A series of 5 successive 5 minutes counts was performed and the count rate at the 511 keV region of interest was recorded. The MDA (minimum detectable activity) of the *in vivo* technique was calculated based on the average count rate observed in the spectra of 23 non-exposed individuals previously monitored for 30 minutes at the IRD- whole body counter.

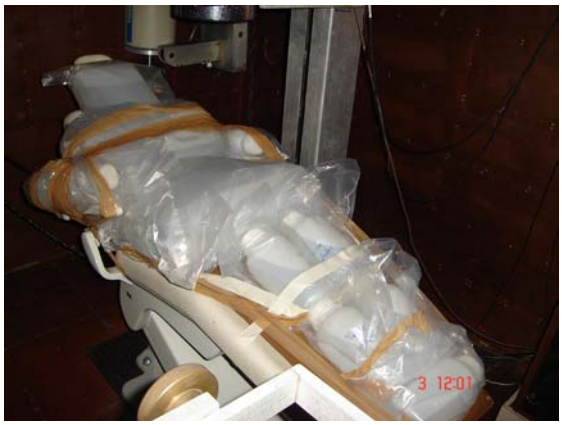

Figure 1. Whole body phantom positioned for the calibration in the IRD whole body counter

For the calibration of the *in vivo* measurement technique aimed to estimate incorporation of ^{18}FDG, it was assembled a brain phantom consisting on a plastic bag containing 1.1 liter of 1 Molar HNO3 spiked with 17.0 ± 0.1 kBq of 22Na standard liquid source. After sealing, the plastic bag was inserted in an artificial resin-based skull. This geometry was chosen due to the high uptake of ^{18}FDG by the brain. The brain phantom was positioned on the torso phantom and measured with a NaI (Tl) 3"x 3" scintillation detector, as presented in the Figure 2. The MDA was calculated based on five spectra of non-exposed individuals measured for 15 minutes in head geometry.

Interpretation of bioassay data

The available data on the biokinetic models for fluoride and ^{18}FDG supplied by the International Commission on Radiological Protection (ICRP) have been edited with the software AIDE-version 6.0 (2). The edition of the biokinetic models permits the obtention of the excretion and retention fractions as a function of time after incorporation, m(t), and also the dose coefficients appropriate for each incorporation scenario. This information is the basis for the calculation of the minimum detectable effective dose (MDED) of each technique. Such parameter is the criteria to evaluate the suitability of the technique to be applied in monitoring programs aimed to evaluate internal exposures.

According to ICRP publication 53, the skeleton rapidly takes up fluoride where it remains for a time, which is considered long in comparison with the radioactive half-life of ^{18}F. The model also establishes that 50% which is taken up by the skeleton is deposited on bone surfaces with uptake half-time of 20 minutes where it is assumed to be retained permanently. The remaining fraction of 50% is eliminated by the renal system within a few hours (6).

Regarding the interpretation of bioassay data for ^{18}FDG, it was edited the biokinetic model suggested by ICRP publication 53. According to the model, ^{18}FDG is transferred rapidly from blood to body cells. Percentages of 4 and 6% are taken up by myocardium and brain, respectively, with an uptake half time of 8 minutes and retained for a time considered long in relation to the radioactive half-life of ^{18}F. From the residual activity in the total body, 60% is assumed to be uniformly distributed amongst all tissues other than brain and heart. A fraction of 30% is assumed to be eliminated by the renal system within few hours (6).

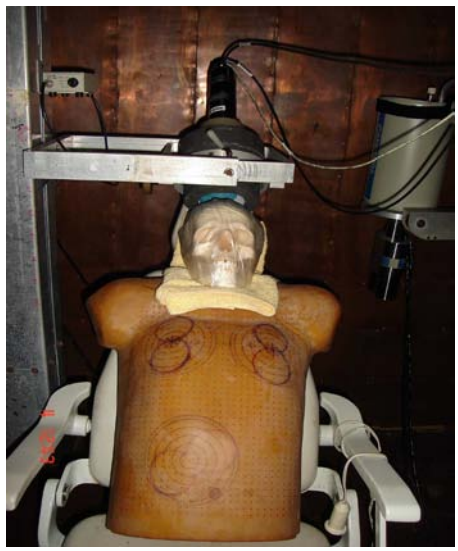

Figure 2. Brain phantom inserted in the resin skull positioned for the measurements

RESULTS

Calibration procedures for in vivo determination of ^{18}F incorporation

Table I presents the results of the calibration of *in vivo* measurement in terms of Calibration Factors, Minimum Detectable Activities (MDA) and Minimum Detectable Effective Doses (MDED). The MDA is calculated for 30 minutes counting time. Calibration factors were calculated based on an average count rate of 5 countings of 5 min.

Table I. Calibration results for *in vivo* measurement techniques

Geometry	Calibration Factor (cpm/Bq)	MDA (Bq)	MDED (mSv)
Whole Body	0.40 ± 0.02	32	4.4×10^{-6}
Brain	0.737 ± 0.005	7.5	1.55×10^{-5}

It is observed that *in vivo* measurement procedures developed in this work are suitable for the evaluation of fluoride and ^{18}FDG incorporation since the techniques present enough sensitivity to detect doses below the recording level of 1 mSv. The minimum detectable effective doses for fluoride and ^{18}FDG were estimated for *in vivo* measurements performed 0.1 day (2.4 hours) after the occurrence of a single intake by ingestion, assuming the higher retention fraction in skeleton and brain, respectively for the fluoride and ^{18}FDG.

Calibration procedures for in vitro determination of ^{18}F incorporation

Table II presents the results of the *in vitro* calibration procedures, in terms of Calibration Factor in the volume range from 100 to 1000 mL, Minimum Detectable Activity (MDA) for 15 min counting time and associated Minimum Detectable Effective Doses (MDED) for fluoride and ^{18}FDG.

The minimum detectable effective doses for fluoride were estimated for a sample collected 0.2 day (4.8 hours) after the occurrence of a single intake by inhalation. Based on the ICRP biokinetic model, this is the time after intake when it is observed the higher excretion fraction in urine. In the case of ^{18}FDG, the minimum detectable effective doses were estimated at 0.1 day (2.4 hours) after a single incorporation by ingestion.

As shown in Table II, the minimum detectable effective doses for fluoride are much higher than the recording level of 1 mSv. This is explained by the fact that fluoride ions are poorly excreted by urine. Therefore, *in vitro* measurements are not suitable to estimate incorporation of ^{18}F in the form of fluoride ions.

On the other hand, results show that *in vitro* measurements are efficient for monitoring accidental intakes of ^{18}FDG. In this case, minimum detectable effective doses are below 1 mSv for a single intake by ingestion for urine samples collected up to about 24 hours after the accident.

Table II. Calibration results for *in vitro* determination of ^{18}F incorporation

Volume (mL)	Calibration Factor (cpm/Bq)	MDA (Bq)	MDED (mSv)	
			Fluoride	^{18}FDG
100	2.15	0.97	1.7×10^{9}	8.0×10^{-7}
200	1.72	1.21	2.2×10^{9}	9.9×10^{-7}
300	1.41	1.48	2.7×10^{9}	1.2×10^{-6}
400	1.19	1.75	3.2×10^{9}	1.4×10^{-6}
500	1.01	2.06	3.8×10^{9}	1.7×10^{-6}
600	0.88	2.37	4.3×10^{9}	1.9×10^{-6}
700	0.79	2.64	4.8×10^{9}	2.1×10^{-6}
800	0.71	2.94	5.4×10^{9}	2.4×10^{-6}
900	0.64	3.26	6.0×10^{9}	2.7×10^{-6}
1000	0.58	3.60	6.6×10^{9}	3.0×10^{-6}

DISCUSSION

In vivo measurements in whole body and brain geometries are suitable to evaluate ^{18}F incorporation in the form of fluoride and ^{18}FDG, respectively. The techniques present enough sensitivity to detect and quantify activities as low as 32 Bq in the whole body and 7.5 Bq in brain, resulting in minimum detectable effective doses of 4.4×10^{-6} and 1.55×10^{-5} mSv, respectively, for fluoride and ^{18}FDG incorporations.

In vitro bioassay showed insufficient sensitivity for the evaluation of fluoride incorporation. However, the technique is able to detect doses below 1 mSv in the case of ^{18}FDG incorporation. In this case it is possible to detect incorporations that would deliver an effective dose of 3.0×10^{-6} mSv, which is far below the recording level of 1 mSv recommended by the IAEA (5).

The use of both *in vivo* and *in vitro* bioassay data in cases of suspicion of incorporation of ^{18}F in the form of ^{18}FDG, permits to determine, with less uncertainty, the form of the compound involved in the accident, the time of incorporation and the route of intake. This is possible by comparing the ratio between whole body, brain and urine activities to the ratio between retention and excretion fractions in those compartments, derived from the biokinetic models suggested by ICRP.

Based on the excretion rates derived from the biokinetic models of fluoride and ^{18}FDG, if ^{18}F is detected in urine samples after a suspicion of accident, it is likely that the radionuclide has

been incorporated in the form of ^{18}FDG. It is then recommended to use brain activity, determined through *in vivo* measurement in skull geometry to estimate intake and effective doses.

If the result of *in vitro* bioassay is below detection limit in a sample of urine it is recommended to calculate intake and dose based on *in vivo* measurement in whole body geometry, because the likelihood that ions fluoride have been incorporated is greater.

Due mainly to the short physical half-life of ^{18}F, the establishment of a routine internal monitoring programme for ^{18}F is not feasible. When considering such possibility, one should consider that after 24 hours the fraction of activity still present in the body would be less than 0.01% of the original intake value. Therefore, an internal monitoring programme for ^{18}F would require a daily frequency of monitoring, which implies in great difficulties to be implemented. For the same reason, in cases of suspected incorporation by ^{18}F, the internal monitoring should be done as soon as possible, in the same day of the incorporation.

REFERENCES

1. Arcoverde, S., Novo equipamento ciclotron produzirá radiofármacos para o nordeste. *Ministério da Ciência e tecnologia-Agência CT*, 2006. Available at :http://agenciact.mct.gov.br/index.php/content/view/24874.html.

2. Bertelli L, Melo DR, Lipsztein J, Cruz-Suarez R. AIDE: Internal Dosimetry Software.Radiation Protection Dosimetry 130, n. 3: 358–367; 20083.

3. Delacroix, D., Guerre, J.P., Leblanc, P. and Hickman C., *Radionuclide and Radiation Protection Data Handbook*, Nuclear Technology Publishing, Oxford, 1998.

4. Ge Medical System Benelux S.A - *Technical Publications Version II*, Last update: September 2004 - TRACERlab MX FDG, Cap 7: Description of the Chemical Process.

5. International Atomic Energy Agency (IAEA). *Occupational Radiation Protection*. Safety Guide N°. RS-G-1.1, 1999.

6. International Commission on Radiological Protection. ICRP, Publication 53.*Radiation Dose to Patients from Radiopharmaceuticals*, 1987.

7. Lomeña, F., Gámez, C., Caberra, A., Maldonado, A. and Jimenez, A. Formación continuada: PET y oncologia. Sociedad Española de Medicina Nuclear, 2006.

8. Oliveira, R., Santos, D., Ferreira, D., Coelho, P.M. B., Veiga, F., Preparações Radiofarmacêuticas e suas aplicações. *Brazilian Journal of Pharmaceut. Science.* 2006, **42**: 151-165.

9. Robillota C. C., A Tomografia por Emissão de pósitrons: uma nova realidade na medicina nuclear brasileira. *Rev. Panam Salud Publica*. 2006; 20:134-42.

10. Sánches, P., PET Radiopharmaceut.. *Revista Espanhola de Medicina Nuclear*, 2001; 20: 477-498.

11. Araujo F., Rebelo A. M. O., Pereira A. C., Moura M. B., Lucena E. A., Dantas A. L. A., Dantas B. M. and Corbo R., Optimization of ^{131}I doses for the treatment of hyperthyroidism**.** *Cell. Mol. Biol*. 2009, **55**: 1-6.

12. Santos A. M. and Vieira J. W., 'Voxelization' of alderson-rando phantom for use in numerical dose measuring. *Cell. Mol. Biol*. 2009, **55**: 7-12.

13. Cardoso J. C. S., Berti e. A. R. and Xavier M., Whole-body measurements at IPEN, Brazil. *Cell. Mol. Biol*. 2009, **55**: 13-15.

14. Vieira J. W. and Lima F. R. A., a software to digital image processing to be used in the voxel phantom development. *Cell. Mol. Biol*. 2009, **55**: 16-22.

15. Holanda C. M. C. X., Silva-Júnior m. F., Alves R. C., Barbosa V. S. A., Silva R. P., Rocha L. G. and Medeiros A. C., The effect of the rochagan™ on radiolabeling with ^{99m}Tc. *Cell. Mol. Biol*. 2009, **55**: 23-28.