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Production and Use of the Radiopharmaceuticals (^{18}F-FDG and ^{18}F-NaF) in Nuclear Medicine in Kazakhstan

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Abstract. This paper presents the results of studies using radiotracer "solution [18F] - fluorodeoxyglucose" with the use of PET/CT method. Calibration studies were performed for PET/CT machine with ^{22}Na source; installation of PET/CT scanner was performed and the program Topas-Vicro was studied to eliminate artefacts arising during operation, the possibility of formation of artefacts was excluded in the study and definition of the ellipse of the head in brain research. On the basis of the application of labeled ultra-short living radionuclides (^{18}F-FDG), malignant tumours and metastases were identified in the bodies of patients.

The article presents information about first experience of production and use of a new radiopharmaceutical ^{18}F-NaF in Kazakhstan for diagnosis of bone metastases of different aetiology by positron-emission/computed tomography (PET/CT).

1 Introduction

The successes of atomic physics have great influence on the development of almost all branches of human knowledge [1,2]. Acquisition of atomic energy has given new means and methods of scientific research into the hands of scientists of diverse specialities. Possibility of scientific knowledge immeasurably increased. Since its inception, scientific medicine draws new ideas and tools for prevention and control over disease in physics and chemistry. It is worth recalling, for example, the opening X-rays at the end of the last century led to the fact that even a small hospital cannot do without X-ray machine now. Use of nuclear energy is of paramount importance for the medicine. This branch of science has been enriched with new, highly valuable methods for studying life processes, diagnosis and treatment of disease. The scope of the mass use of radionuclides is nuclear medicine. Radionuclides are used in nuclear medicine, mainly in the form of radiopharmaceuticals (RPCs) for the early diagnosis of diseases of various organs and for therapy.

RPC is a chemical compound containing certain radioactive nuclide in the molecule allowed for administration to humans for diagnostic or therapeutic purposes. At the same time, a distinctive feature of the diagnostic RPC is the lack of pharmacological effect [3,4].

Bone metastases are frequent complication of a whole number of tumour diseases, in the first place of breast cancer, prostate cancer, lung cancer, renal cancer, thyroid carcinoma. Bone metastases are one of the factors, which considerably lower the life quality, that is why their early detection and treatment remain actual problem in oncology up till now.

Application of new RPC with high sensitivity and specificity to pathological changes of osseous tissue will extend limitations of cancer patients diagnosis.

The aim of this work is the production and use of labeled positron-emitting ultra-short living radionuclides for the radioisotope diagnosis using the positron emission tomography.

This paper presents the results on the production and use of RPC "fluorodeoxyglucose, ^{18}F" in Astana on the basis of JSC National Diagnostic Center to diagnose complex oncological, neurological and cardiovascular diseases.

RPC "fluorodeoxyglucose, ^{18}F" is used as a diagnostic tool for the positron emission tomography (PET). The main indications for the study are:

- in oncology: the differential diagnosis of malignant tumours of different clinical forms and localization, including tumours of the brain, determining the prevalence and staging of malignant tumours, evaluation of tumour treatment;

- in cardiology: evaluation of myocardial viability in the planning of reconstructive surgery in patients with coronary artery disease and left ventricular systolic dysfunction, monitoring the effectiveness of treatment of myocardium;

- in neurology: identifying hypometabolism in epilepsy centers, the differential diagnosis of parkinsonism, determining the degree of brain damage in traumatic brain injury and cerebrovascular disease, determining the effectiveness of treatment of neurological and neuropsychiatric diseases.

Contraindications. Specific contraindication to the use of the drug was found. Using the RPC "fluorodeoxyglucose, ^{18}F" contraindicated during pregnancy and lactation.

2 Methodology of Research

The main research method was the method of positron emission tomography (PET) – the newest method based on the use of ultra-short living radioisotopes. PET is an essential component of a cyclotron, which yields labeled positron-emitting RPCs [5].

At present, the series of first experimental data on the production of the RPC (^{18}F-FDG) were obtained. Research is carried out using the methods of PET/CT and SPECT.

Radionuclide of fluorine-18 is produced by irradiation of the nuclei of the isotope of oxygen-18 by beam of accelerated protons with an energy of 15 MeV according to the reaction:

$$^{18}\mathrm{O}(p,n)^{18}\mathrm{F}\,.$$

As a target substance, water enriched with oxygen-18 is used. Produced radionuclide of fluorine-18 is stabilized in the chemical form of fluoride, fluorine-18 ([^{18}F], F).

2.1 Formation of radionuclides of nitrogen-13 and fluorine-17

With the indicated parameters of irradiation, oxygen-16 and oxygen-17, contained in the irradiated material as impurities, undergo nuclear reactions with the formation of radionuclides of nitrogen-13 (half-life - 9,96 min) and fluorine-17 (half-life - 70 s), respectively:

$$^{16}\mathrm{O}(p,\alpha)^{13}\mathrm{N}$$
$$^{17}\mathrm{O}(p,n)^{17}\mathrm{F}\,.$$

Chemical forms of stabilization of nitrogen-13 is nitrogen gas [^{13}N]N_2. Radionuclide of fluorine-17 is stabilized in the chemical form of fluoride, fluorine-17.

The content of nitrogen-13 and fluorine-17 in preparation at the time of its manufacture cannot exceed 0.01% theoretically, which allows not identifying radionuclide impurities in the final product.

Production of fluoride tetrabutylammonium, fluorine-18:

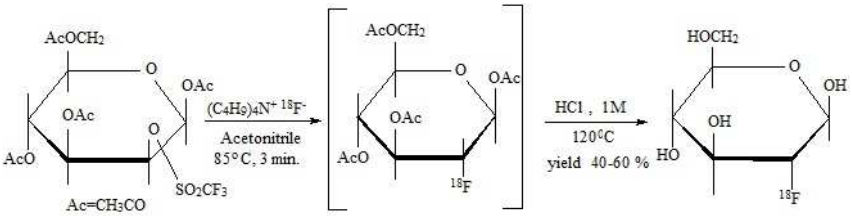
$$\underbrace{(C_4H_9)_4N^+HCO_3^-}_{\substack{\text{Tetrabutylammonium}\\ \text{hydrocarbonate}\\ \text{M.m 303}}} + \underbrace{{}^{18}F^-}_{\substack{\text{Fluoride,}\\ \text{fluorine-18}\\ \text{A.m 18}}} \xrightarrow[H_2O]{} \underbrace{(C_4H_9)_4N^{+18}F^-}_{\substack{\text{Tetrabutylammonium}\\ \text{fluoride, fluorine-18}\\ \text{M.m 260}}} + \underbrace{HCO_3^-}_{\substack{\text{Hydrocarbonate}\\ \text{M.m 61}}}$$

Adverse reaction. Formation of chloride tetrabutylammonium:

$$\underbrace{(C_4H_9)_4N^+HCO_3^-}_{\text{Tetrabutylammonium hydrocarbonate M.m 303}} + \underbrace{Cl^-}_{\text{Chloride, A.m 35}}$$

$$\xrightarrow[H_2O]{} \underbrace{(C_4H_9)_4N^+Cl^-}_{\text{Tetrabutylammonium chloride M.m 277}} + \underbrace{HCO_3^-}_{\text{Hydrocarbonate M.m 61}}$$

Preparation of 2-fluoro [^{18}F]-2-deoxy-D-glucose:

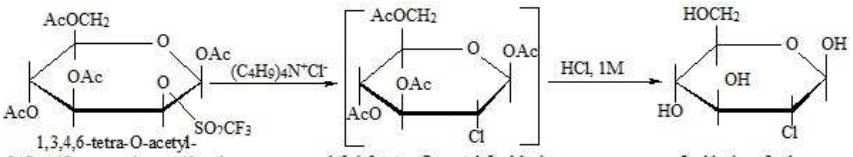


1,3,4,6-tetra-O-acetyl-2-O- trifluoromethanesulfonyl-β-D- mannopyranose Mm. 480

1,3,4,6-tetra-O-acetyl-2-fluorine [^{18}F]-2-deoxy-β-D- glucopyranose Mm. 349

2-fluorine [^{18}F]-2-deoxy-β-D- glucopyranose Mm. 181 (2-fluorine [^{18}F]-2-deoxy-D-glucose)

The formation of 2-chloro-2-deoxy-β-D-glucopyranose:

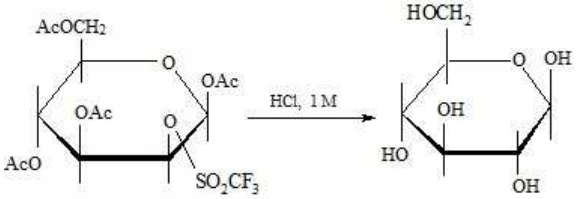


1,3,4,6-tetra-O-acetyl-2-O- trifluoromethanesulfonyl-β-D- mannopyranose Mm. 480

1,3,4,6-tetra-O-acetyl-2-chlorine 2- deoxy-β-D- glucopyranose Mm. 366

2-chlorine- 2- deoxy-β-D- glucopyranose Mm. 198

The formation of D-glucose:



1,3,4,6-tetra-O-acetyl-2-O- trifluoromethanesulfonyl-β-D- mannopyranose Mm. 480

D-glucose

2.2 "Fluorodeoxyglucose, ^{18}F"

"Fluorodeoxyglucose, ^{18}F" is a nonspecific tumour-tropic RPC and accumulates in high quantities in the cells of malignant tumours and metastases due to their inherent hyperglycolysis [6-10]. ^{18}F fluorodeoxyglucose accumulation level in cancer cells correlates with the degree of their malignancy. The product also allows to evaluate the effect of the treatment, since the level of drug accumulation in tumours is reduced in effective treatment and it does not change or increases in ineffective one. ^{18}F fluorodeoxyglucose is actively transported into the cells by proteins-transporters, where it undergoes phosphorylation to form fluorodeoxyglucose-6-phosphate, ^{18}F, the product which does not enter further reactions and is retained in this form in the cells of malignant tumours. In the non-transformed cells of tissues and organs, dephosphorylation is observed to form fluorodeoxyglucose, ^{18}F, which is derived from normal cells and can be redistributed. The best conditions for the detection of malignant tumours are the mild hypoglycaemia achieved by starvation for 4-6 hours, and the water load (intake of 500 - 800 ml of water) after the introduction of the RPC. Patients are asked to empty the bladder several times. Starvation promotes increased glucose uptake by the cells, and water load accelerates the removal of the label from normal tissues in the urine, thereby reducing the level of radioactivity and radiation exposure. For patients with diabetes, it is necessary to control the blood glucose level before the study. PET study is only performed when the blood glucose level is normal or low.

After intravenous administration of the drug, ^{18}F fluorodeoxyglucose quickly leaves the bloodstream and gradually builds up in organs and tissues. ^{18}F fluorodeoxyglucose is excreted by the kidneys to the bladder, so the pelvis of the kidneys, ureters and bladder are also visualized normally. More than 50% of the injected amount of radiotracer is excreted in the urine within the first 2 hours after injection. In the brain, increased accumulation of radiotracer is observed in the cortex and deeper structures, and the content of the RPC in the gray matter is 2 times higher than in white one. Accumulation of the drug in human myocardium is 3-4% of the administered one. Optimal ratio of organ/background in the study of infarction and brain is reached after 35-40 minutes after the intravenous administration of the drug and continues for another 25-30 minutes which is sufficient for positron emission tomography. Optimal ratio of tumour/normal tissue is observed 45-120 minutes after drug administration and persists for another 240-360 minutes after administration [11-13].

Glucose, containing radioactive atom, is used in PET/CT. The generated radioactivity is registered in special chamber. Since malignant cells have an increased metabolism, they consume large quantity of radioactive glucose. PET/CT with ^{18}F-FDG allows us to detect tumour in a whole body within one examination. In some cases given method makes it possible to separate benign and malignant tumours. Sometimes for better diagnosis of certain kinds of cancer PET is combined with CT (PET/CT method). However, PET/CT with the use of ^{18}F-

FDG is mainly sensitive to osteolytic bone metastases. Osteoblastic metastases do not consume glucose.

2.3 PET/CT with ^{18}F-NaF

PET/CT with ^{18}F-NaF bone scanning with the help of introduction of radioactive material NaF with isotope ^{18}18F is used for effective diagnosis of osteoblastic and osteolytic types of bone metastases, for determination of their disposition and size, for definition of spread of disease. This method allows us to carry out differential diagnosis between malignant and benign as well as other bone affections, such as: Backache or unexplainable bone pains:

1. Osteomyelitis;
2. Inflammatory and degenerative arthritises;
3. Aseptic necrosis;
4. Osteonecrosis of lower jaw;
5. Paget's disease;
6. Bone graft viability;
7. Joint implant complications.

PET/CT scanning with ^{18}F-NaF has higher diagnostic accuracy than ordinary bone scanning with 99mTc, and also advantages are the major contraction of scanning time, diagnosis both osteoblastic and osteolytic types of bone metastases. All the skeletal system is scanned and bones image with high resolution is created during the PET/CT scanning with sodium fluoride injection. PET/CT with marker ^{18}F-NaF is applied for diagnosis of bone metastases. Advantages of this method in comparison with conventional skeletal scintigraphy are higher spatial resolution and 3D investigation technique, therefore ^{18}F-NaF PET/CT makes it possible to detect the smallest bone metastases.

Table 1. Comparison characteristic of the methods

♯	Investigation method	Sensitivity	Specificity
1	Planar scintigraphy	54%	88%
2	Planar + SPEKT	92%	100%
3	^{18}F Fluoride PET	100%	100%

3 Results and Discussion

As it is well known, more than 90% of the Positron Emission Tomography is performed with an analog of glucose fluorodeoxyglucose, in which a stable fluorine is replaced by the radioactive one, resulting in ultra-short living radiopharmaceutical of 18-fluorodeoxyglucose – ^{18}FDG [I.G. Zubal *et al*, Ratio

images calculated from interictal positron emission tomography and singlephoton emission computed tomography for quantification of the uncouplingof brain metabolismand perfusin in epilepsy, *Epilepsia* **41** (2000) 1560-66].

In this work, we have carried out a research with the PET/CT using the RPC "solution [^{18}F] - fluorodeoxyglucose" and intravenous maintenance for the diagnosis of complex oncological diseases by PET/CT according to the testimony.

Calibration studies were performed for PET/CT machine with ^{22}Na source. PET scanner was installed and the program Topas-Vicro was studied to eliminate artefacts arising during the work. Any artefact was prevented in the study and definition of the ellipse of head in the studies of brain.

TOPAS-VICRO toolkit was studied for smoothing model and experimental noise. Currently we perform a two-dimensional visualization of the original projections (sinogram) or the solution - tomograms. Herewith, one-dimensional graphics are built for any horizontal or vertical section of image. Solving problems on one-dimensional deconvolution is based on such components as one-dimensional Fourier and wavelet analysis and filtering of external or internal (tomogram) matrices, two-dimensional Fourier analysis of the tomograms or external images, one-dimensional smoothing and differentiation over the rows or columns of the image. Reconstruction results are saved in the image and binary formats [14,15].

The investigation of patients was performed and corresponding PET/CT pictures of patients were obtained. The analysis and interpretation of these data were performed; appropriate conclusions were obtained and prepared: using ultra-short living tracer radionuclide (^{18}F-FDG), malignant tumours and metastases were detected in the bodies of patients. The resulting radionuclide based on 18 F – FDG reveals bone metastases (PET-CT picture).

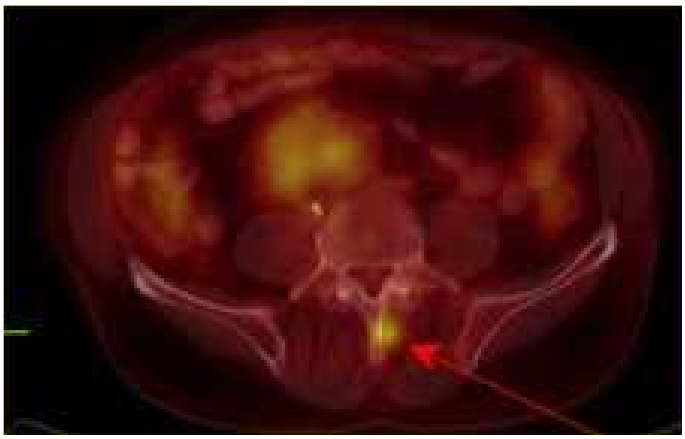


Figure 1. Patient P.P. Bone metastases: in the left acetabulum in the spinous process 4 of the lumbar vertebra.

The Control Committee of Medical and Pharmaceutical activity of the Ministry of Healthcare and Social Development of the Republic of Kazakhstan gave permission as of 25.04.2014 ♯ 002/6692 to production and use of new RPC - ^{18}F-NaF.

3.1 Production

^{18}F isotope is produced in a cyclotron "Cyclone 18/9" (IBA) using the nuclear reaction ^{18}O(p,n)^{18}F. Niobium target with a volume of 2 ml, filled with water, enriched by the isotope ^{18}O, is irradiated by a proton beam with a current of 30 mkA on the target. The solution, containing ^{18}F, is pumped into automated synthesis module Synthera (IBA), with prepared kit for production of Na^{18}F (ABX). Ions of ^{18}F are trapped by column Sep Pak Light Accell Plus QMA, then the column is washed with 0.9% solution of NaCl. At the final stage, 2 ml Na^{18}F moves into a sterile pyrogen-free vial through 0.22 micron filter.

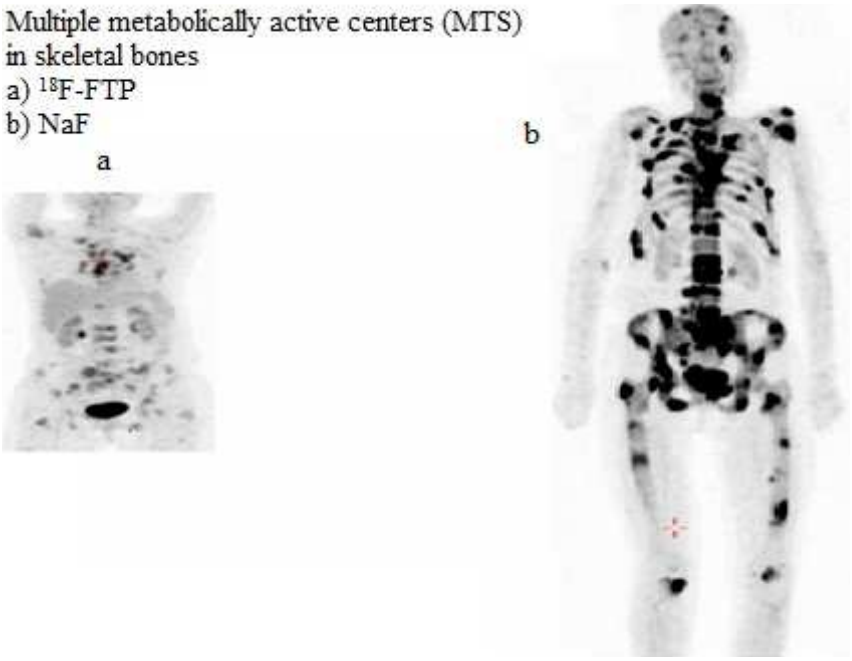
3.2 Quality control

The pH value of the solution Na^{18}F is measured with the use of pH test strips (0-14), which change their color depending on pH-sample. The results are estimated by standard buffer solution with well-known pH. The radiochemical purity of the solution Na^{18}F is estimated using thin-layer chromatography (TLC). Stationary phase of TLC is silica gel, mobile phase is mixture - acetonitrile : water (95:5% by volume). The peak of radioactivity is determined by scanning of a silica gel plate with a collimated detector (Minigita, Raytest). Radionuclidic purity is determined by gamma-ray spectrometer ("Mucha", Raytest). A half-life of the isotope ^{18}F is calculated after measuring the activity of the sample within 20 minutes ("Unidos 4", PTW Freiburg).

3.3 Procedure for examination

A small amount of slightly radioactive substance (^{18}F-NaF) is injected intravenously to the patient. The scanning on PET/CT is started after 30 minutes, it takes about 20 minutes. And contrast medium is not injected. The dose for an adult is 185-370 MBq (5-10 mCi). The higher activity (370 MBq, 10 mCi) can be used to obese patients. The radionuclide activity for children must be calculated on the basis of weight (2.22 MBq/kg, 0.06 mCi/kg) with the use of minimum and maximum activity from 18.5 to 185 MBq (0.5 to 5 mCi).

The 19 examinations on PET/CT with the use of new RPC ^{18}F-NaF were carried out in the Department of Radionuclide diagnostics. All the patients were referred with the diagnosis: "Breast cancer, prostate cancer, bone metastases without primary lesion, agnogenic bone pains". The 10 patients were examined on PET/CT with ^{18}F-FDG and the 9 patients were examined on gamma camera with the use of Tc-99m. It was revealed by investigation results: metastases in bones of skeleton are confirmed in 12 (63.1%) patients; degenerative or dystrophic changes of skeletal system are diagnosed in 7 (36.8%) patients. New pathological focuses were revealed in 5 (41.6%) of 12 patients.



This is our first experience of production and application of new RPC for the diagnosis of bone lesions. However, even small amount of studies allowed us to assess the sensitivity and specificity of the drug in comparison with other RPCs.

4 Conclusions

Thus, we have performed:

- calibration study of PET/CT machine with ^{22}Na source;
- installation of PET/CT scanner and studying the Topas-Vicro program to avoid artefacts arising at work; prevent any artefacts in the study and definition of a head ellipse in the study of a brain;
- malignant tumours and metastases in the bodies of patients were identified by applying labeled ultra-short living radionuclides (^{18}F-FDG) [16, 17].

Studying literary sources and relying on our first experience, we can conclude, that examinations on PET/CT with ^{18}F-sodium fluoride (NaF) have a number of advantages in comparison with conventional 99mTc on SPECT and PET/CT with ^{18}F-FDG, such as:

- the higher accuracy in detection of osteolytic and osteoblastic metastases;
- differentiation between benign and malignant tumours;

- differentiation of degenerative and dystrophic changes from malignant;
- the higher sensitivity in comparison with 99mTc and ^{18}F-FDG;
- the higher specificity in comparison with 99mTc and ^{18}F-FDG;
- precise anatomic information, received from CT-component;
- three-dimensional and whole body scanning, similar to investigations on PET/CT with FDG;
- RPC ^{18}F-sodium fluoride (NaF) is easily available for use;
- the value of the achievements in the field of nuclear medicine is identifying the diseases not diagnosed by other methods at an early stage when the cure is possible, as well as improvement of the condition and extension of lives of seriously ill patients;
- in most cases, the use of radioisotope diagnosis helps to save lives of patients with such complex cancer as tumours of various etiologies including brain cancer, lymphoma, leukaemia, etc., when other means are not effective [18, 19].

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