Generators and automated generator systems for production and on-line injections of pet radiopharmaceuticals

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Abstract. One of the prospective directions of PET development is using generator positron radiating nuclides [1,2]. Introduction of this technology is financially promising, since it does not require expensive special accelerator and radiochemical laboratory in the medical institution, which considerably reduces costs of PET diagnostics and makes it available to more patients. POZITOM-PRO RPC LLC developed and produced an $^{82}\text{Sr}^{82}\text{Rb}$ generator, an automated injection system, designed for automatic and fully-controlled injections of $^{82}\text{RbCl}$ produced by this generator, automated radiopharmaceutical synthesis units based on generated $^{68}\text{Ga}$ produced using a domestically-manufactured $^{68}\text{Ge}^{68}\text{Ga}$ generator for preparing two pharmaceuticals: Ga-68-DOTA-TATE and Vascular Ga-68.

1. Introduction
Presently, an efficient offer is equipping fully functional PET centers and medical institutions that have PET scanners with radionuclide generator systems, in particular, $^{68}\text{Ge}^{68}\text{Ga}$ and $^{82}\text{Sr}^{82}\text{Rb}$, to generate positron radiating radionuclides and radiopharmaceuticals based on them which notably expands the range of PET method application in clinical practice.

Radionuclide generator is a rather compact device with own protection from ionizing radiation. Its operation does not require to specially design and then provide maintenance for complex specialized rooms systems, like with accelerator equipment.

2. Radionuclide generator system construction
Radionuclide medical generator is an installation in which the long-lived (mother) nuclides are used to generate other (daughter) nuclides with shorter half-life, in the form of pharmaceutically acceptable (or compatible with it) in vivo medical preparation.

By method of nuclide pair separation extraction and chromatographic generators are distinguished. In extraction generators nuclide pair separation is performed by extracting the required nuclide into an appropriate solvent.

However, in practical terms chromatographic generators, where parent radionuclide is fixed on mineral or organic sorbent, are more process-efficient. Daughter radionuclide is extracted by eluting from the column with an appropriate solvent (eluent).

Number of possible extractions (elutions) depends on the life duration of mother radionuclide. Daughter radionuclide extraction rate depends on how quickly the equilibrium is achieved. If the daughter radionuclide half-life is negligibly short compared to the mother radionuclide, then 50% of
the equilibrium amount is accumulated by the end of the first half-life, 75% by the end of the second half-life and 99% by the end of 6 half-lives. Consequently, eluate from a generator with short-lived daughter radionuclide may be obtained as frequently as needed.

3. Radionuclide generator system $^{82}$Sr/$^{82}$Rb

In cardiovascular disease diagnostics, myocardial blood flow condition evaluation is of great importance [3]. Absorption of $^{82}$Rb$^+$ is evaluated by blood flow, the condition of Na$^+-$K$^+$/ATP pump and integrity of cellular membrane. For this reason, already from the first attempts of using it as an alternative for $^{15}$N$\text{NH}_3$, it was introduced in non-invasive myocardial blood flow measurements by PET, as well as for visualization of functional changes connected with cerebral blood circulation condition evaluation in various cerebral diseases diagnostics.

$^{82}$Rb$^+$ can be used for qualitative and quantitative evaluation of cerebral cells’ integrity, which is particularly important to obtain clearer outline of cerebral tumors distribution and to distinguish tumors and to evaluate radiation necrosis when radiation treatments are introduced.

$[^{82}\text{Rb}]\text{RbCl}$, apart from the simplicity of generation process, has a number of other advantages, as it has short half-life (76 seconds). Besides this, not only is the patient radiation exposure reduced, but several stress tests can be performed consecutively, which leads to shorter test duration and getting a more objective picture of the condition.

Procedure duration at rest and with a pharmaceutical sample is not over 30 minutes, while a full-scale myocardial perfusion exam with any other known method of diagnostic nuclear medicine would require more time.

4. Radionuclide generator system $^{68}$Ge/$^{68}$Ga

Perspectives for $^{68}$Ga ($[^{68}\text{Ga}]\text{DOTATOC}$)-labeled pharmaceuticals for neuroendocrine malignant tumor diagnostics may be estimated by analyzing an earlier preparation version based on $^{111}$In. ($[^{111}\text{In}]\text{-DTPA-D-Phe}^1\text{-Tyr}^3\text{-octreotide}$) [4]. This pharmaceutical helps to diagnose a broad range of diseases not only of neuroendocrine nature, which increases interest in similar $^{68}$Ga-labeled predecessors. In evaluating the disease diagnostics efficiency on the equivalent objects, positron emitting radionuclide $^{68}$Ga-labeled pharmaceuticals have demonstrated higher sensitivity due to conceptually different detection scheme. Detection principle is different from that of SPECT, it involves lead collimators, and it accounts for higher sensitivity of PET.

Radionuclide generator system has optimal characteristics of the mother and daughter radionuclides. Mother radionuclide half-life (271 days) ensures efficient generator performance for about 1 year, with the possibility to obtain daughter radionuclide each 4 hours (70% from the initial potency).

$^{68}$Ga radionuclide may be used to label more proteins, peptides and small molecules. Half-life is 68 minutes, which ensured higher diagnostics efficiency without additional radiation exposure for patients.

5. Automated injection system

A pharmaceutical obtained from the generators described above may be injected directly intravenously (generator system $82$Sr/$82$Rb) or after additional treatment (generator system $68$Ge/$68$Ga). For these procedures in clinical practice, there has been developed and manufactured an automated injection system [5] (see figure 1), which is an automated system of solution infusion, including: means to produce a solution; means for infusion; means for radioactive solution dosing based on potency level or volume; means of automatic monitoring for current potency, occlusion, weight and solution radioactivity in the waste container; own protection from ionizing radiation. Infusion process is fully automated.
In order to enhance the potential of the automated injection system, POZITOM-PRO RPC LLC has developed and pilot tested an automated radiopharmaceutical synthesis module based on generated Ga-68. The designed automated radiopharmaceutical synthesis module based on generated Ga-68 produces preparations from domestically produced lyophilizates, to produce two pharmaceuticals: Ga-68-DOTA-TATE and Vascular Ga-68. Preclinical studies of these pharmaceuticals are conducted together with the Federal State Institution A. I. Burnazyan Federal Medical and Biophysical Center.

6. Conclusions
Radionuclide generator system is a rather compact device with individual protection from ionizing radiation. Its main advantage is that it does not depend on cyclotron and can be installed in medical institutions with only PET scanners available. Introduction of the generator technology for radiopharmaceutical production is also financially attractive, as costly accelerator equipment and a radiochemical laboratory are not needed in this case, which considerably reduces cost of PET diagnostics and makes it affordable to a big part of the population of the Russian Federation.

The described automated injection system helps facilitate generator systems usage, ensure precision and automation of needed activity selection, reduce personnel and patient radiation exposure, and ensure control over all operation processes.

References
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