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01. Country Report

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Development of Radiopharmacy and Current Status of Radioisotopes and Radiopharmaceuticals Production in North Macedonia

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Background

Nuclear medicine and radiopharmacy have a 60-year tradition in Macedonia (North Macedonia since February 2019). The national strategy accompanied by the support of the IAEA, led to the gradual and reliable progress of radiopharmacy in the country, which resulted in an increase in the range of radiopharmaceuticals used in clinical practice, with the establishment of the production of PET radioisotopes and radiopharmaceuticals.

Beginnings and development of conventional radio pharmacy

The early stages of nuclear medicine in Macedonia date back to the late 1950s,

specifically 1958, when the first dose of iodine-131 was ordered and received, thus beginning the application of radioactive isotopes for medical purposes in Macedonia. Two years earlier, in 1956, the Medical Faculty in Skopje decided that the Center for the Application of Radioactive Isotopes in Medicine in Macedonia should be located at the Institute of Pathophysiology at the Medical Faculty at the "Ss Cyril and Methodius" University in Skopje. Between 1944 and 1991, Macedonia was part of the Yugoslav federation, so the establishment of the Center for the Application of Radioactive Isotopes for Medical Purposes began as a result of the implementation of the Federal Nuclear Energy Commission's program to establish such centers in every Yugoslav republic. As part of the Center for the Application of Radioactive Isotopes, within the Institute of Pathophysiology and Nuclear Medicine, as one of its organizational units, the Laboratory of radio pharmacy and radioimmunology for the preparation of radioactive preparations, used for nuclear medicine, clinical and research purposes, became operational. In the first few years, the institute used to import radioactive preparations, but as early as 1960, radio labelling techniques began to be implemented in the laboratory. The first preparations made were iodine-131 preparations, namely [^{131}I]NaI, [^{131}I]iodohippurate, Rose Bengal labelled with iodine-131, plasma proteins in vitro labelled with iodine-131 and autologous erythrocytes labelled with chromium-51 in anemia (a test to determine erythrocyte life and hepatic and splenic index). Iodine-131 in the form of an oral solution for the treatment of thyroid disease and phosphorus-32 for polycythemia were used for therapy. For the needs of the thyroid examinations, as well as for the scientific research work related to the etiopathogenesis of thyroid diseases, a laboratory for hormonal analysis was set up. Among the first tests to assess thyroid status was the determination of plasma-bound radioiodine (iodine-131) by butanol extraction, and in the late 1960s a triiodothyronine test was introduced, with adsorption of unbound triiodothyronine labelled with iodine-131 to activated carbon. Determination of thyroxine by the competitive, protein-binding method began in the early 1970s. In 1978, the radioimmunoassay method for the determination of thyroxine was introduced, and the radioiodination of thyroxine with the radionuclide iodine-125 used to be performed in the laboratory, together with the preparation of all necessary reagents for analysis. The same year, the radioimmunoassay method for the determination of TSH with commercial reagents was introduced. In the 1980s, tests on other hormones began. Until the mid-1990s, RIA and IRMA methods were used for hormonal analysis. Nowadays, these tests are mainly performed with an automatic immunoassay analyzer.

In the 1970s, the import of ^{99}Mo/^{99m}Tc generators and the radiolabelling with metastable technetium (technetium-99m) began. Activities related to the preparation of non-radioactive kits and their labelling with technetium-99m and appropriate quality control

(radiochemical purity, radionuclide purity, sterility, apirogenicity) were started in the radio pharmacy laboratory .

The first preparations used for diagnostic imaging were the first-generation technetium radiopharmaceuticals, namely [^{99m}Tc]Tc-DTPA, [^{99m}Tc]Tc-DMSA, [^{99m}Tc]Tc-MAA, [^{99m}Tc]Tc-Pyrophosphate and [^{99m}Tc]Tc-Sulfur Colloid. Since 1997, the second generation technetium radiopharmaceuticals, namely [^{99m}Tc]Tc-MDP, [^{99m}Tc]Tc-MIBI, [^{99m}Tc]Tc-HMPAO, [^{99m}Tc]Tc-MAG3, [^{99m}Tc]Tc-HIDA (and derivatives), [^{99m}Tc]Tc-ECD and [^{99m}Tc]Tc-HSA, have been routinely used. The techniques of radio labelling autologous erythrocytes, leukocytes, and platelets (to a lesser extent) have become routine practice. At the end of the 1990s, the radiopharmaceutical laboratory was reconstructed and reorganized in order to adhere to legal regulations. Current efforts in the field of radio pharmacy at the Institute of Pathophysiology and Nuclear Medicine in Skopje are technetium-99m labelled peptides. The Institute of Pathophysiology and Nuclear Medicine in Skopje was the only institution to carry out activities in the fields of nuclear medicine and radio pharmacy in the country, until the mid-1980s when at the Medical Center in Bitola, the Department of Nuclear Medicine went operational, in which a laboratory of radio pharmacy was set up. At the moment, two public health nuclear departments in two different towns are being developed. Additionally, at the Faculty of Medical Sciences at the University Goce Delchev Stip, a radio pharmacy laboratory has already been established, wherein research activities related to radio labelling monoclonal antibodies have been carried out.

Beginning of PET radiopharmacy

In Macedonia, the first PET/CT examinations using of [^{18}F]FDG were performed in Acibadem Sistina hospital in 2014. However, the production of PET radiopharmaceuticals started at the University Institute of Positron Emission Tomography (UI PET), which is at the moment, the only institution that produces PET radionuclides in the country or indeed in the region. UI PET is a public health institution for the production of radioisotopes and radiopharmaceuticals, and the diagnosis of metabolic functional changes using positron-emission tomography. The construction of UI PET facility was started in November 2013. The Institute is currently equipped with a 16,5 MeV GE PET Trace 800 cyclotron with targets for the production of fluorine-18, carbon-11 and nitrogen-13. There is a possibility of additional embedding of solid targets. The department for the production of radiopharmaceuticals is designed and constructed in accordance with the principles of Good Manufacturing Practice (GMP) and compliance with the European regulations for the production of PET radiopharmaceuticals. In this facility, there are three production laboratories, namely the [^{18}F]FDG laboratory, the laboratory for other PET radiodiagnostics and the laboratory for

radiotherapeutics and orphan drugs in the classified area. In addition, there are two quality control laboratories as well as a research laboratory. An environmental monitoring system for gaseous and liquid waste and the BMS (Building Management System) which enables the continuous control of temperature, humidity and pressures in the production area, are implemented in the facility. December 2015 heralded the first productions of radioisotopes (fluorine-18, carbon-11 and nitrogen-13) in Macedonia. After the qualification of the equipment (the HVAC system and monitoring systems), UI PET obtained a license from the Radiation Safety Directorate as well as a GMP license from the National Agency for Medicines and Medical Devices for production, quality control and sales of radiopharmaceuticals, that was issued on the basis of the criteria met in terms of facility, equipment and personnel, in accordance with national legislation. In June 2017, UI PET started routine in-house production of [^{18}F] FDG for its use in PET/CT diagnostics.

Conclusion

Currently, the radio pharmacy and the nuclear medicine activities are performed in five institutions in the country (three public and two private health institutions). Two additional public health nuclear medicine departments are under development as well. 99Mo/99mTc generators are imported, but radiolabelling and quality control procedures are routinely conducted in-house in the corresponding centers. In the field of conventional nuclear medicine, iodine-131 and technetium-99m radiopharmaceuticals have become well established for use in clinical practice. Regarding PET radiopharmaceuticals, [^{18}F]FDG is regularly used in every center equipped with PET/CT cameras. UI PET is the only institution in the country which produces fluorine-18 radioisotope and the [^{18}F]FDG radiopharmaceutical. Presently, one of the major efforts for radio pharmacy in Macedonia is enriching the product range with other radiopharmaceuticals that can be successfully implemented in nuclear medical clinical practice.

Picture 1. Laboratories for the production of radiopharmaceuticals (UI PET, Skopje)

Reference:

Nuclear Medicine in Macedonia 1956 – 2016, *Prof. Dr. Borislav Karanfilski and associates (Macedonian Medical Association, Macedonian Association of Nuclear Medicine),* December 2016

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