The use of $^{19}$F in Medicine in Poland and in the World

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Abstract: Fluorine is a chemical element belonging to the group of halogens. Due to its many properties, it has been used in various fields of medicine, mainly in dentistry, pharmacology, oncology, and radiology. It is an element that occurs naturally in the environment with a very high chemical activity. In addition, it has a high affinity for calcium or magnesium [1], which may have a large impact on the body's functioning when a higher dose of fluoride is taken. Moreover, fluorine is an element that has toxic effects, not only on living organisms but also on the environment. Fluoride-based preparations are widely used in several areas of medicine. This paper presents the use of fluoride in its various branches of medicine.

Keywords: fluorine; $^{19}$F MRI; fluorinated drugs.

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1. Introduction

Fluorine is a chemical element that is essential for proper functioning. It is found in many foods, in water, and some medications. It should be remembered that the excessive concentration of this element in the body is extremely toxic and leads to many undesirable effects, such as magnesium malabsorption, weakening of the skeletal system, negative impact on the nervous system. Sabraoui et al., based on the research, found that methanol extract (PPE) from pomegranate peel (Punica granatum. L) showed a protective effect on fluorine-induced toxicity in protozoa Tetrahymena pyriformis [2].

Figure 1. Fields of medicine related to fluorine.
2. Fluoride in Medicine

The possibilities of using fluorine in medicine are getting wider every year. Various fields of medicine are based on the use of this element in their activities. When analyzing the PubMed article database, it can be noticed that the number of publications on the use of fluoride in medicine is increasing every year. The figure below shows the areas of medicine that include the field of application of fluorine.

3. Dentistry

One of the main areas of application in dentistry is related to the positive influence of fluorine ions on the inhibition of enamel demineralization and the ability to mineralize through the exchange of the enamel and dentin building blocks. Wierichs et al., in their research, described the effect of the effectiveness of using different fluorine concentrations on the remineralization and demineralization of dentin [3]. In addition, fluorine has an antibacterial effect, which may positively affect the elimination and inhibition of the growth of bacteria causing caries. Hence, the reports of adding fluorine to drinking water and commonly available toothpaste may inhibit the development of caries in society. In addition, there are mouthwashes on the market that contain fluoride ions and dental gels and medications. Avenetti et al. group, in their research, checked the effect of the use of fluoridated toothpaste in children under three years of age in Chicago [4]. Whereas Wu et al. investigated the effectiveness of fluoride varnish on the first molars and its effect on caries, they concluded that using varnish with 5% sodium fluoride was more effective in preventing caries than education in the field of oral hygiene [5]. Attention should also be paid to the treatment with silver diamine fluoride (SDF-silver diamine fluoride), which positively affects the arrest of caries in children [6]. However, one should remember the negative effects of therapy and pay attention to the doses received. In their research, Bernstein et al. described the use of SDF in primary dental care among African Americans with limited access to dental offices [7]. Pirca group et al. assessed the effect of toothpaste containing amorphous casein phosphate with phosphopeptide (FPC-FCA) and sodium fluoride on the erosion of tooth enamel. It was concluded that the FPC-FCA complex showed greater remineralizing effects than sodium fluoride [8]. The group of Tomiyama et al. assessed the effect of toothpaste containing an ion-releasing filler, which inhibited dentin demineralization and showed the effect of shortening the viability of bacteria [9]. Wang et al. assessed the positive and negative effects of the use of fluoridated toothpaste and awareness among dentists [10]. In dentistry, a number of fluorine varnishes are used to prevent tooth decay. The group of Pichaiaukrit et al. examined a varnish containing chitosan, which is to prolong the release of fluorine, which may result in a better effect in preventing caries, but the varnishes turned out to be cytotoxic to gingival fibroblasts [11].

On the other hand, the group of Pauli et al. implemented studies to assess the effect of iontophoresis on the uptake of fluoride in enamel. Different electric currents were applied, and analyzing the research, it was concluded that the use of iontophoresis at 0.8 mA with a fluorinated gel (2% NaF) increased the fluoride uptake in enamel with carious lesions [12]. In their research, the group of Bröseler et al. assessed the P 11 -4 peptide; based on the research, and it was found that there was a significant reduction in carious lesions in patients [13]. Studies have also shown that silver diaminofluorine in combination with potassium iodide can re-harden early carious lesions [14].
4. Pharmacology

The pharmaceutical market includes many drugs that contain fluorine nuclei. In 1957, the first fluorinated drug, 5-fluorouracil (5-FU), was introduced to the market [15]. However, fludrocortisone was the first to be obtained in 1954. 5-FU is used, among other things, in studies in patients with liver metastases of colorectal cancer [16]. In recent studies, Zhdanov et al. described the disturbance of signaling pathways dependent on NF-κB, cAMP, and the MAPK cascade in the regulation of granulocytopenias under the influence of treatment with 5-fluorouracil [17]. In 1977, perfluorocarbon compounds (PFCs) were introduced and analyzed for the first time by MRI 19F. The implementation of PFC research may contribute to the development of research in drug distribution using the 19F MRI technique because, in PFCs, hydrogen atoms replace fluorine atoms. Also, drug delivery systems based on nanotechnology can help develop new pharmaceuticals [18].

PFCs emulsify and can carry drugs [19]. Fluorine resonance can play an important role in treatment tracking and therapy monitoring, thanks to the use of 19F in pharmacotherapy, including through cell biodistribution. Scientific research on drugs using MRI also contributes to understanding metabolic properties and their cytotoxicity. Implementing research using the 19F MRS technique may allow the monitoring of drug supply and its metabolism. Fluorinated drugs used in pharmacology have gained great popularity in various conditions. The most popular of them, used in various therapeutic groups, will be discussed below.

In addition, because fluorine is an element that plays an important role in the process of bone tissue formation, it is used in the treatment of osteoporosis. Thanks to its properties, it can stimulate osteoblast proliferation and thus inhibit the activity of osteoclasts, which results in the inhibition of the formation of bone defects and stimulation to strengthen bone tissue. In their research, Liu et al. showed that the hydroxyapatite contained in fluoride inhibits bone resorption [20].

One of the popular drugs containing fluoride is the anticancer drug 5-fluorouracil, which is used in the chemotherapy of malignant neoplasms such as breast [21], stomach [22], pancreas [23], colon [24], and rectal cancer [25]. Brix et al., in their research in 1995, investigated the biodistribution and catabolism of this drug in in vivo studies in rats with cancerous tumors. In order to be able to visualize the drug selectively, the studies used the CHESS 19F MR imaging technique with a chemical shift [26]. In subsequent studies, Brix et al. implemented the dynamic technique of 18F PET (positron emission tomography) assessing biodistribution and 19F MRI to check metabolism. The studies were performed on rats with hepatomas implanted, and on the basis of the performed MR studies, information was obtained about the metabolism of 5-FU, which is converted into FBAL only within the liver, and not in lesions [27]. Mapping 5-FU and assessing its metabolites is informative. It turned out that increasing the sensitivity of imaging due to an additional 90-degree pulse in the FSE sequence significantly improves the signal-to-noise ratio in the 19F 5-FU images in animal studies [28]. The most recent studies show automatic quality control of PET [18 F] -FDOPA imaging using connected two different convolutional neural networks [29].

A significant proportion of drugs used in psychiatric therapy are sedatives and anxiolytics. The use of fluoride in pharmaceuticals of this type improves the absorption of drugs, thanks to which it is possible to use a lower dose of the drug. An example of an antipsychotic drug is fluphenazine (fluphenazine), a drug used in the treatment of, for example, schizophrenia [30]. In vivo and in vitro studies of this drug using 19F MRI and MRS techniques
were carried out by the group of Arndt et al. 1988, checking the biodistribution of this drug in studies on rats [31]. Another fluorinated drug is fluorodopa (FDOPA), which is most often used as a "radiotracker" in PET [32]. By contrast, Girard et al. presented the FDOPA study to classify gliomas by PET / CT [33]. Other studies have shown a comparable or slightly higher uptake of $^{18}$F FDOPA H compared to $^{18}$F FDOPA-L, uptake in patients with neuroendocrine tumors [34].

On the other hand, Yanagisawa et al. in their research they used it as a 19F MRI probe in a Parkinson's disease model in studies on rats using a 7 Tesla scanner [35]. Another drug is perfluorodecalin (PFD), which has an oxygenating effect; Gewiese et al., in 1992, carried out 19F MRI examinations that enabled imaging of the drug with the use of a magnetic resonance imaging system that enables fluorine imaging [36]. Also, Noske et al., in 1993, detected residual PFD in a human eye undergoing vitreoretinal surgery using 19F MRI [37]. In contrast, Gulyaev et al. used perfluorodecalin, conducted in vivo studies on rats to identify a drug for the 19F MRI oximetry method; the studies confirmed the possibility of using this drug [38]. Another investigational drug is trastuzumab, which is used to treat HER2 overexpressing breast cancer. Bartusik et al. describe the use of 19F MRI in their research to test the efficacy of fluorinated trastuzumab in 3D cell cultures [39]. Moreover, studies on detecting labeled trastuzumab by cellular 19F MRI in ex vivo studies were presented [40].

On the other hand, Constantinides et al. assessed the temporal accumulation and localization of the drug isoflurane (ISO) in mice in vivo 19F MRS [41]. There are also reports of the use of 19F MRS and chemical shift imaging (CSI) to study the drug haloperidol in patients with schizophrenia [42]. Wang et al., in their work, presented fluoride-containing anesthetics, and based on a summary of drugs, they described the toxicity and safety of drugs from various therapeutic groups [43].

5. Therapies

Early diagnosis and implementation of an appropriate treatment regimen as well as monitoring of the applied therapies at the earliest stage of cancer, for example, with the use of antibody therapy in ex vivo studies, turn out to be extremely important [44]. Anticancer drugs in tumors and the liver are related to drug accumulation and metabolism. It turns out that it is important to implement tests that allow assessing the kinetics of drugs. Presant et al., in their research they extended this assessment in vivo studies; thanks to the use of 19F NMR it is possible to monitor the therapy [45]. In their research, de Forni et al. studied the cardiotoxicity of intravenous fluorouracil in high doses, also in combination with other drugs, and alone, the frequency of adverse effects was 7.6% [46]. Studies also show the evaluation of intracellular and extracellular fluorouracil in studies with gadolinium-based contrast enhancement [47]. Ikehira et al. conducted a 19F MRS study of the pharmacokinetics of drugs based on 5-FU using a 1.5 T MR scanner [48]. The studies also show the possibility of predicting the chemotherapeutic response in patients with colorectal metastases to therapy using gadolinium-DTPA enhancement and the 19F MRS method. Still, no clear correlation was found [49]. In the case of patients treated with fluoxetine, the concentration in the human brain, based on the conducted MRS studies, is up to 10.7 micrograms/ml in the human brain, and in relation to plasma, it is 20: 1 in animal studies [50]. There are many reports in the scientific literature on labeling anticancer agents with 19F. Sotak et al. describes perfluoro-2,2,2',2'-tetramethyl-4,4'-bis-1,3-dioxolane in his research as a new perfluorocarbon for use in 19F MR and 19F MRS imaging [51]. On the other hand, Spees et al. demonstrate the usefulness of 19F-labeled
methotrexate for predicting a therapeutic response based on the differentiation of susceptible and resistant neoplastic lesions [52].

On the other hand, Du et al. used 19F-labeled micelles as drug delivery agents in chemotherapy [53]. The group of van Gorp et al. using 7T resonance and transceiver coils and the 19F technique, MRS evaluated capecitabine (Cap) used in cancer treatment or in palliative treatment. Drug metabolism was assessed to investigate drug metabolism and toxicity, and the group showed great potential for research [54].

In the case of drugs used in the treatment of mental diseases, it is possible to use the 19F isotope in NMRS research because it is one of the components of such drugs. An example may be the concentration of fluoxetine and trifluoperazine in the brain [55]. Furthermore, controlling the level of tissue oxygenation can be used to evaluate and optimize anticancer therapies or to implement further medical procedures, for example, in the case of wound healing. Nöth et al. used quantitative 19F MRI in vivo to determine oxygen in perfluorocarbons using alginate capsules that were implanted in rats into various tissues, including the peritoneal cavity [56].

In other studies, Wang et al. implemented in vivo studies using two computed tomography (KT) techniques and 19F MRI of perfluorinated encapsulated mesenchymal stem cells [43]. In other studies, Richard et al. assessed the possibility of labeling (PFC) human glial stem cells based on cell culture studies [57]. Koshkin et al., in the latest research, presented polymeric nanoparticles filled with perfluorocarbons for multimodal imaging in vivo research. Nanoparticles were used for imaging dendritic cells by means of ultrasound and 19F MRI [58].

In contrast, Gaudet et al. used the technique of double-labeling human mesenchymal stem cells (hMSC) and their monitoring with 19F MRI in vivo studies in mice, which enables the simultaneous tracking of two populations of cells, which may contribute to determining the causes of transplant failure [59]. 19F MRI enables the detection and quantification of stem cells in vivo tests, which may be a tool for the early evaluation of therapeutic cell delivery [60]. The group of Gonzales et al., in their studies, presented the use of 19F MRI and 19F MRS to track in vivo labeled PFC cells in mice in the liver, lung, and spleen [61]. Studies also show clinical 19F MRI tracking of a PFC tracer for dendritic cell therapy (DC) patients with colorectal adenocarcinoma [62].

Fluorinated dendrimers are used more and more frequently in studies, which enable high sensitivity in 19F MRI tests [63].

6. Diagnostic Imaging

The use of fluoride nuclei in medical imaging has become more and more popular in recent years. Due to its properties, fluoride is increasingly used in magnetic resonance imaging diagnosis. Despite the fact that the basic nucleus fulfilling the resonance condition is hydrogen in 1H MRI imaging, which is used in clinical devices. There is also the possibility of imaging other elements, such as fluorine 19F, but also the carbon 13C isotope, phosphorus 31P, 15N, oxygen 17O, sodium 23Na. The composition of the human body determines the use of hydrogen resonance in clinical diagnostics because it is the most numerous. However, due to the similar resonant frequency, the fluorine nucleus is more and more often used in scientific work [64,65]. The spectrum of 19F MRI applications includes such tests as monitoring delivered drugs, monitoring the progress of therapy, or diagnosing pathological changes, including cancer, spectroscopic tests including 19F-labeled anticancer drugs. Many reports from cell culture studies show a controlled way to study cellular and molecular properties. 19F MRI enables
selective signal collection and thus imaging without a tissue background [66], which turns out to be extremely important in the case of research on pharmaceutical substances. They enable, among other things, monitoring of drug delivery [67], assessment of metabolism, tracing of labeled cells [68-70], and the possibility of visualization of new fluorinated drug conjugates [39]. The use of various forms of the drug in research and its modifications, inter alia, with a fluorine compound, allows the use of 19F MRI fluorine resonance, which would allow imaging of the drug without background and direct quantitative measurement, thanks to which it will be possible to try to transfer the results of in vitro tests to in vivo tests. Fluorinated particles can also act as markers or contrast agents in MRI. In addition, there are many studies of preparations containing fluorine particles, for example, anesthetics, and studies of the determination of fluoride in blood plasma. Recent reports talk about molecular and cellular imaging, including targeted therapies using immune and stem cells and cell tracking on MRI.

7. 19F MRI.

Thanks to the use of a strong magnetic field and electromagnetic waves in the range of radio waves, it is possible to study the properties of the tested matter in a non-invasive way. In conventional magnetic resonance imaging (MR) using 1H hydrogen nuclei, we obtain data-carrying morphological information from the examined area, while 19F MRI (magnetic resonance imaging) collects the signal only from these nuclei. Thus, it is possible to imagine without a tissue background. Fluorine magnetic resonance, therefore, enables selective imaging, which can be used, for example, to monitor the delivered drugs, monitor the progress of therapy, or diagnose pathological changes, including neoplasms. There are many applications of fluorine molecules in the literature in the form of nanoemulsions, perfluorocarbons (PFCs), fluorinated drugs, and other tracking agents. In this review, we present a literature review of the use of 19F MRI in medicine in Poland and around the world, paying special attention to the use of fluorinated drugs and clinical diagnostics with the use of 19F, in addition, we describe the prospects for the use of 19F in the future. PFCs delivered to the lungs in the form of an aerosol offer the possibility of imaging with 19F MRI [71]. Schwarz et al., in 1999, reported research on perfluoronone as a new contrast agent in 19F MRI imaging in gastrointestinal imaging in animal studies [72]. 19F MRI enables selective imaging of drugs by using the chemical shift technique (CSI) of, for example, the drug 5-FU and its major catabolite, alpha-fluoro-beta-alanine (FBAL) [73]. The development of a specific MR imaging technique may contribute to the non-invasive monitoring of drugs and their metabolism in pathological changes in vivo studies [74]. Langereis et al. developed a temperature-sensitive liposomal contrast agent 1H CEST and 19F for drug delivery under MR control [75]. An interesting marker in vivo imaging is the PLGA perfluorocarbon nanoparticles used in 19F MRI of various populations of cells in a clinical setting [76]. On the other hand, the group of scientists Nakamura et al. developed a new drug delivery vehicle based on mesoporous silica nanoparticles (MSN). The anticancer drug (doxorubicin, DOX) was "locked" inside nanoparticles functionalized with folate, thus enabling intracellular therapy [77].

8. 18F PET.

Positron emission tomography (PET) is a diagnostic method used in molecular diagnostics to assess radioactivity. It consists of an intravenous injection of a radiopharmaceutical, which biodistributes depending on the chemical properties and activities...
of the area under study. As a result of the annihilation of the electron-positron pair, the spatial distribution of the emission of photons of high-energy electromagnetic radiation with the energy of 511 keV is determined. The most widely used radiopharmaceutical is $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG). As a glucose analog, it is transported from the blood into cells mainly by GLUT1. Based on the difference in metabolism between a healthy cell and a cancer cell with a higher energy requirement. The implementation of the $^{18}$F PET technique in combination with $^{19}$F MRI is a good tool to assess the biodistribution and metabolism of 5-fluorouracil [27]. Maynard et al. used in their research the PET technique of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG PET) as a non-invasive pharmacodynamic biomarker [78]. One should also pay attention to the popular $^{18}$F-FDG PET/CT examination, which combines two imaging techniques. In the first stage, a so-called "low dose" computed tomography is performed, and then a PET scan is performed, then the fusion of two images is performed. This type of examination is a good tool for assessing neoplastic changes in the patient's body.

9. Conclusions

The number of publications on $^{19}$F over the years has remained very high, especially when it comes to $^{19}$F MRI; one can notice a rapidly growing interest in scientific research. Both $^{19}$F MRI and $^{19}$F MRS publications in vivo and in vitro studies are constantly increasing. Fluoride is characterized by high sensitivity in magnetic resonance; it is about 83% in relation to hydrogen. Therefore it can be widely used in MR imaging, hence the growing interest in this type of research. Monitoring drugs at the cellular level is a key step in developing new targeted therapies. Studies in three-dimensional cell cultures may directly influence the development of in vivo studies. Moreover, it is interesting to study the use of fluorinated drugs, contrast agents, and dendrimers, which have many more advantages over the commonly used pharmaceuticals. An additional advantage may be the possibility of imaging without a tissue background, which makes it possible to quantify a drug or a fluorine-based contrast agent in vivo tests. One should also pay attention to multi-channel devices that have the possibility of classical imaging of hydrogen nuclei and fluorine nuclei, such a "hybrid" enables two-channel imaging, based on which, after creating image fusion, we have an ideal diagnostic technique that may be widely used in the future. The continuous development of research using $^{19}$F MRI may significantly influence the development of research in the field of treatment monitoring in neoplastic diseases, evaluation of the effectiveness of therapy, and the development of specialized drug carriers, which will contribute to more effective treatment. In vivo testing with $^{19}$F MRI could contribute to drug therapies. For example, Bo et al. developed doxorubicin (DOX) tracking in mice using the $^{19}$F MRI technique [79]. New approaches have the potential to significantly optimize the delivery and monitoring of various types of drugs in vivo testing using the non-invasive $^{19}$F MRI method.

Funding

This research received no external funding.

Acknowledgments

Declared none.
Conflicts of Interest

None.

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