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BIOPHYSICS AND MEDICAL PHYSICS

The Effect of an Iodine-Free Diet on the Pharmacokinetics of the ^{211}At Preparation

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Abstract—The pharmacokinetics of the Astatine-211 radiopharmaceutical was investigated after a single injection in male SD (Sprague–Dawley) rats that had normal and iodine-free diets. Twelve groups of SD male rats were examined in the study. The tested drug was intravenously injected into the tail vein of the animals once at a volume of 10 mL/kg and dose of 100 μCi per animal. In the study, the animals were subjected to necropsy at specific time points with retrieval of the organs and tissues for further analysis of the activity of the samples using a well-type scintillation gamma spectrometer. It was found that the ^{211}At absorption by the thyroid in the male rats that had an iodine-free diet was greater than in the rats that had a conventional diet.

Keywords: radiopharmaceuticals, alpha emitters, pharmacokinetics, gamma spectrometry.

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INTRODUCTION

The Astatine-211 radiopharmaceutical is a promising candidate for replacement of radiopharmaceuticals that are based on ^{131}I that are used in radioactive iodine therapy [1–3]. In contrast to the ^{131}I beta-emitting radioactive isotope, which is also a source of high-energy gamma radiation (the absorption length of the gamma rays with energy of several hundred kiloelectronvolts in tissues reaches several centimeters) and has a half-life of 8.04 days, the ^{211}At radionuclide has a significantly shorter half-life of 7.24 h and is a source of alpha particles with a free path in tissues of approximately 60 μm, which is equal to several cell diameters. The linear energy transfer for alpha particles with energy from 5 to 8 MeV is approximately 100 keV/μm, which corresponds to the maximum biological effect of the nuclear ionizing radiation. First, these properties of the ^{211}At isotope make it possible to achieve an effect that is similar to radioiodine therapy by introducing an activity that is 20 times lower (which corresponds to a number of introduced radionuclides that is 500 times smaller) and to significantly reduce the radiation load on the patient's body due to the high selectivity and relatively short-term exposure. Second, they make it possible to solve the problem of radiation safety during natural excretion of the preparation from the patient's body (owing to the short half-life of this isotope). Studies on animals demonstrated that Astatine-211 has tropism to the thyroid [4–6]. However, as was mentioned in studies that are devoted to radioiodine therapy many times (see, e.g., [7–9]), the therapy with radioactive iodine requires following an iodine-free diet. Thus, a study of ^{211}At accumulation in the thyroid depending on the duration of the special diet is very important for the development of recommendations for the application of Astatine-211 for treatment of oncological and autoimmune thyroid disorders.

1. MATERIALS AND METHODS

The ^{211}At isotope was generated on a cyclotron of the Skobeltsyn Institute of Nuclear Physics of Moscow State University according to the reaction ^{209}Bi(α, $2n$)^{211}At using a thick (200–300 μm) bismuth target with the natural isotope composition at the energy of the alpha particles of 30 MeV. At this energy, the ^{211}At yield was approximately 1 mCi/(h μA) [4]. The Astatine-211 radiopharmaceutical was synthesized by sublimation of the generated ^{211}At from the irradiated bismuth target at a temperature of 800°C into isotonic

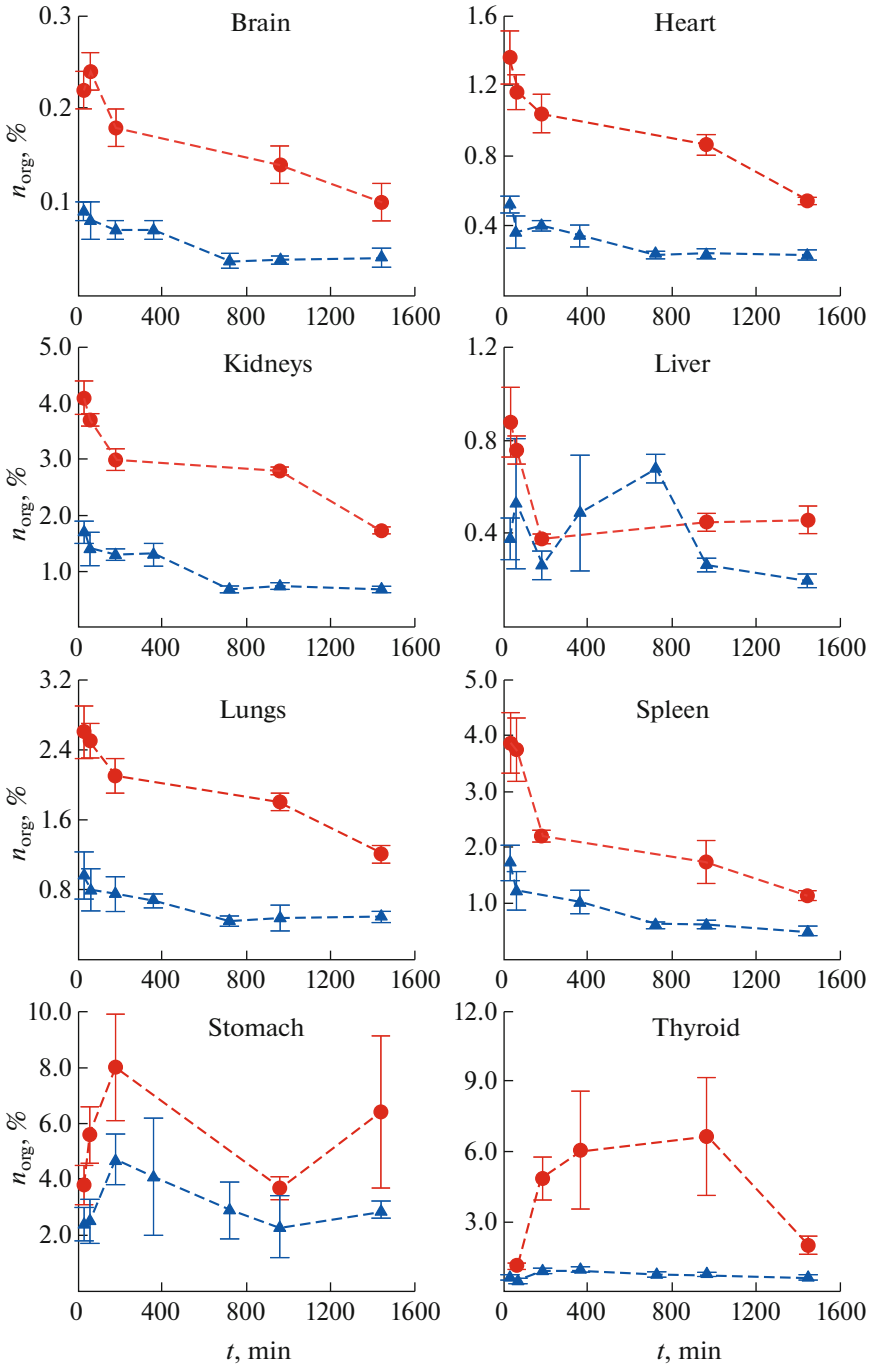

Fig. 1. The dependence of $n_{org}(t)$ for different organs. Blue triangles, an iodine-free diet; red circles, a normal diet. The points are connected with a dotted line.

saline. The radiochemical purity of the generated radiopharmaceutical was measured by gamma spectroscopy using an HpGe detector (energy resolution of 1.5 keV at energy of 661.7 keV (^{137}Cs)). The pharmacokinetics of the Astatine-211 radiopharmaceutical were studied in two animal groups. One group had a normal diet, while the other group had an iodine-free diet for 3 days. To analyze the pharmacokinetics, the tested radiopharmaceutical was intravenously introduced into the tail vein of the animals (male SD (Sprague Dawley) rats) once at a volume of 10 mL/kg and dose of 100 μCi per animal. In the study, the animals were subjected to necropsy at specified time points (30 min, 1 h, 3 h, 6 h, 12 h, 16 h, and 24 h) with the retrieval of organs and tissues for further calculation of the accumulated activity using a well-type scintillation gamma spectrometer. Six animals were used for each time point.

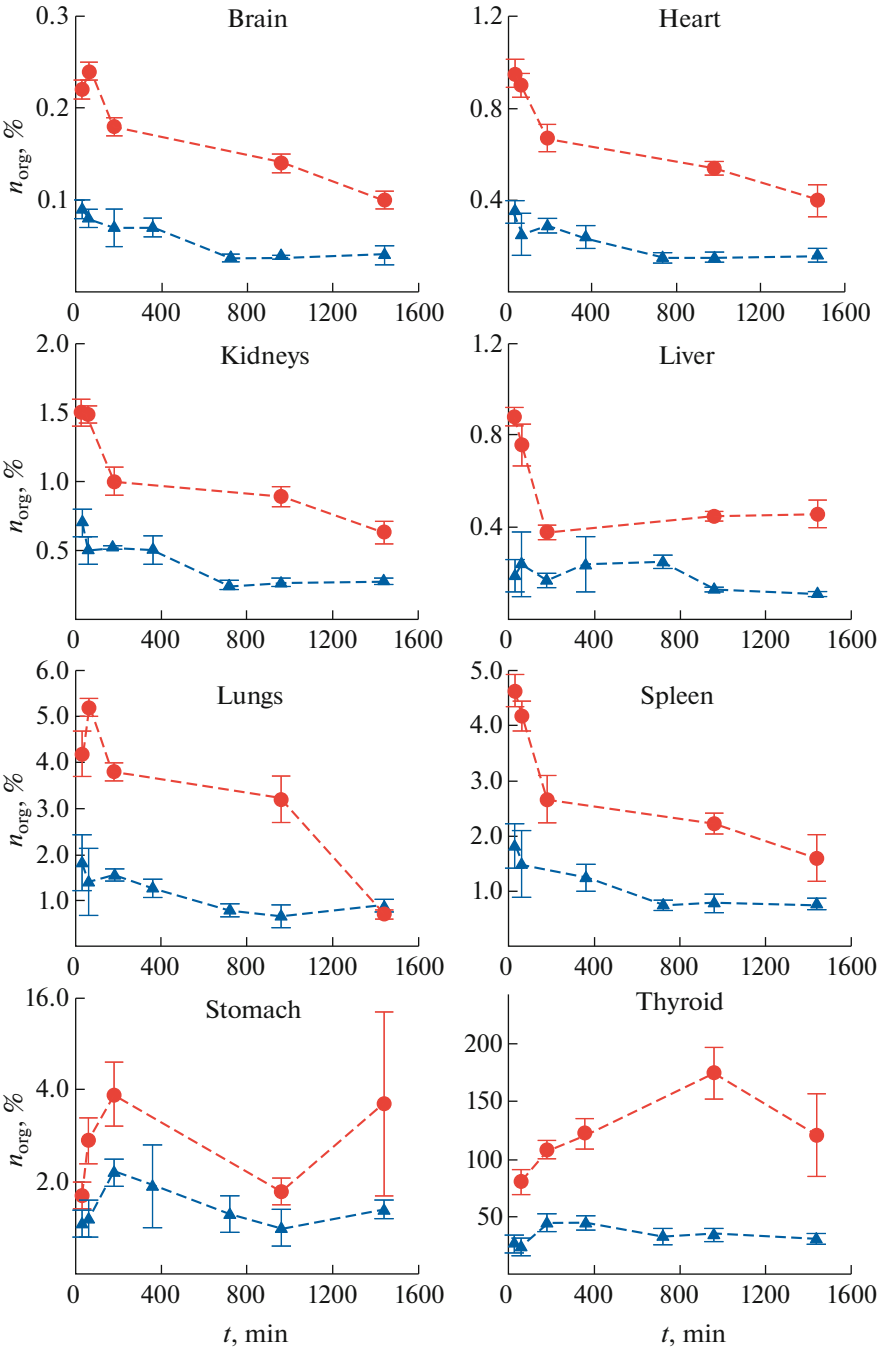

Fig. 2. The dependence of $n_m(t)$ for different organs. For designations see Fig. 1.

The activity in the organs was determined as the percentage of the introduced activity

$$n_{org}(t) = \frac{N_{org}(t)}{N_{inj}} \times 100\% \quad (1)$$

and as the percentage of the introduced activity per organ mass

$$n_m(t) = \frac{n_{org}(t)}{m_{org}}, \quad (2)$$

where $N_{org}(t)$ is the activity in the organ at the time t, N_{inj} is the introduced activity, and m_{org} is the organ mass in grams.

2. RESULTS

The time dependence of the accumulated activity in the percentage of the introduced activity for eight organs (thyroid, spleen, stomach, heart, liver, kidneys, lungs, and brain) of animals that had normal and

iodine-free diets is given in Fig. 1. It can be seen from the figure that of all the critical organs the thyroid has the greatest tropism with respect to Astatine-211. The maximum accumulation of Astatine-211 in the thyroid is achieved 16 h after its introduction. In all other organs except for the stomach, the Astatine-211 concentration decreases with time. Moreover, the iodine-free diet increases the ^{211}At accumulation in all the organs with the greatest increase observed in the thyroid. This is especially clear when we consider the accumulated activity in the organ for the mass of this organ (Fig. 2). The ^{211}At concentration per gram in the thyroid is higher by an order of magnitude than in the other critical organs. The selective ^{211}At accumulation in the thyroid astatine appears to be due to the fact that astatine is a chemical analog of iodine. There is some evidence that iodine is delivered to thyroid cells in the form of NaI [1]. It is unknown whether this symport is used for astatine [8]; however, the astatine tropism to the thyroid may be evidence of similar mechanisms of the delivery of astatine and iodine to the thyroid.

CONCLUSIONS

The pharmacokinetics of the Astatine-211 radiopharmaceutical was studied on male SD (Sprague–Dawley) rats that had a normal diet and a 3-day iodine-free diet. Astatine-211 was found to have tropism to the thyroid in both cases. However, the iodine-free diet led to a concentration of the ^{211}At radionuclide in the thyroid that was several times higher, which can indicate the importance of following an iodine-free diet during treatment with the Astatine-211 radiopharmaceutical. These studies also make it possible to establish the prognostic value of the duration of this diet in the case of medical application of the Astatine-211 radiopharmaceutical for actual patients.

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