ESTIMATION OF THE ABSORBED DOSES OF SYNTHESIZED CISPLATIN WITH ^{195m}Pt IN VARIOUS ORGANS OF ANIMALS

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^{195m}Pt has been obtained in reaction ^{197}Au(γ,np)^{195m}Pt on the electron linear accelerator with energy 40 MeV and current 10 μA. To produce ^{195m}Pt from a target of gold the extractor such as Kuchera-Shtoly was needed. The following stage of technology consisted in obtaining synthetic cisplatin on a basis ^{195m}Pt. The admixture of activity ^{196}Au in synthesized cisplatin was 1.4% relatively of the ^{195m}Pt activity. The effective dozes have been measured in various organs of animals after administration of cisplatin containing ^{195m}Pt with activity 13 kBq. It has been shown that effective dozes from ^{195m}Pt cisplatin for various organs were from 0.72 to 0.20 mGy/MBq.

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1. INTRODUCTION

In recent years a large series of new antineoplastic preparations have been developed. The combination of these drugs with radiotherapy enabled to develop and update the schemes and regimens of their optimal use, as well as, to increase the efficiency of cancer-carrier treatment. In Ukraine the oncologists have in their arsenal more than 70 antineoplastic preparations [1-2]. However, despite the achievements in this field some of these drugs are imperfect and most of them have a low selective action. Therefore, there is an urgent need to develop new pharmaceuticals, update the available ones and to combine the treatment regimens. The main reason for this is a necessity of decreasing the toxic influence of drugs, reducing the painful symptoms and increasing the patient life.

Among the chemical preparations exerting an antitumoral action are the complex compounds of transition metals, in particular, platinum compounds. For the most part, antitumor drags are organic matters by the chemical structure. In this context cisplatin is a premier inorganic and effective antitumor drug. Just the geometrical configuration of platinum complexes plays an important role not only in a sense of changing their physical-mechanical properties, but, also, their biological activity.

Labeling of cisplatin by the ^{195m}Pt isotope makes it possible to use a high value of Auger electron bremsstrahlung losses in the cell nucleus. A synergism influence due to the bystander effect should be noted too. Production of radioactive cisplatin is possible by irradiating prepared pharmaceuticals. In this case the radiation doses not leading to the cisplatin molecule destruction are permissible. In the case of platinum irradiation with high radiation beams a further synthesis of radioactive cisplatin is necessary.

The advantages of ^{195m}Pt use for labeling radiotracers provoked many attempts of ^{195m}Pt synthesis [3]. However, the obtained specific activities (30-50 Bq/mg) of radiotracers have not permitted to reach significant results in the tumor treatment. Successful efforts for production of ^{195m}Pt with a high specific activity were undertaken in the USA, Oak Ridge. By the double neutron capture in the reactor, being the most intense in the world, a specific activity of ^{195m}Pt near 80 mCi/mg was reached [4].

2. PROCEDURE OF ^{195m}Pt EXTRACTION

The article presents and discusses the conditions of cisplatin (Mili Healthcare LC, GB) at 26- and – 34 MeV electron accelerators using the bremsstrahlung. In this case the radioactive cisplatin makes 1000 Bq/mg of cisplatin. At a dose of 5 Gr the destruction of cisplatin molecule occurs that appears in the form of a fine suspension in the preparation. At a dose more than 10 Gr a brown precipitate settles out from cisplatin preparation.

The use of crystalline cisplatin allows one to increase the irradiation dose. At an irradiation dose of more than 10 Gr there occurs significant destruction of the crystalline cisplatin molecule. However, the most part of crystalline cisplatin conserve their structure. After separation of the destroyed cisplatin, the specific activity of radioactive crystalline cisplatin was determined at a level of 2 kBq/mg.

We performed the synthesis of radioactive cisplatin from irradiated samples of crystalline and dissolved cisplatin. By the crystal optic properties the synthesized radioactive cisplatin get some qualities approaching a new formed phase with crystal-hydrate modifications to the initial compound composition.

Brake radiation of the electronic accelerator was used for obtaining ^{195m}Pt by means of an irradiation of gold. Extraction of gold was used for obtaining radioactive cisplatin with high specific activity (about 1 Ci/mg). Nuclear reaction ^{197}Au (γ,np)^{195m}Pt was used. Synthesis of radioactive cisplatin is realized.

Cisplatin of a high specific activity was obtained in the high-current electron accelerator using the nuclear reaction ^{197}Au(γ,np)^{195m}Pt with a threshold of 13.7 MeV. The cross-section of the reaction ^{197}Au(γ,np)^{195m}Pt slowly increases to 100 MeV and according to the estimation at 30 Mev energy has the value of 2 mbn [5]. The output of ^{195m}Pt isomer is near 30%. Therefore the ^{197}Au(γ ,np)^{195m}Pt reaction cross-section for the 30 MeV gamma-quanta is about 0.6 mbn. The reaction ^{197}Au(γ,2p)^{195}Ir → ^{195m}Pt also leads to the ^{195m}Pt production [5]. The ^{196}Au yield in the nuclear reaction ^{197}Au(γ,n)^{196}Au→^{196}Pt exceeds the ^{195m}Pt yield approximately by a factor of 1000. The half-life of ^{196}Au is 6.18 days. Therefore to decrease the ^{196}Pt concentration in the process of radioactive cisplatin production it is necessary to perform a repeated gold extraction from the irradiated target. The maximum

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specific activity of ^{195m}Pt can be 100 Ci/mg. So, by irradiating the gold with bremsstrahlung during 24 hours with the subsequent gold extraction we can obtain the specific activity of ^{195m}Pt at a level of 2 Ci/mg that is significantly higher than the specific activity of ^{195m}Pt obtained by the USA researchers [4]. The gold extraction after four-hour irradiation can give the specific activity of ^{195m}Pt at a level of 10 Ci/mg. Potentialities of the NSC KIPT high-power electron accelerator (34 MeV and 500 μA) make it possible to produce up to 50-100 mCi/day. To obtain ^{195m}Pt of a high specific activity the sample of 1 g weight was irradiated with bremsstrahlung from the accelerator KUT-20 (electron energy of 34 MeV and current of 500 μA) during 5 hours.

Platinum was separated by means of gold extraction. For this purpose the gold sample after irradiation in the accelerator was dissolved in the aqua regia (1:3 – HNO_3:HCl). For the more rapid dissolving we added into the solution several drops of hydrogen peroxide. To remove the nitrogen acid the solution was repeatedly evaporated. Then the gold solution in the 10% hydrochloric acid was prepared. After 20 ml of hydrochloric acid-gold solution were poured into the extractor (Fig.1). Into the flask, being heated up, 100 ml of ethyl acetate were poured. By evaporating ethyl acetate was condensed in the refrigerator and from there it arrived via the glass pipe onto the extractor bottom. Ethyl acetate was running up over the hydrochloric acid-gold solution simultaneously extracting gold. Then ethyl acetate got again into the heated flask with ethyl acetate. Extraction of gold by 100 ml of ethyl acetate has been carried out during 4 hours.

The measurement of the gamma-activity spectrum in this stage showed significant decrease of the ^{196}Au activity (approximately by a factor of 10^4). However, the relative intensity of ^{195m}Pt was insignificant. After this procedure ethyl acetate was removed and the flask was again charged with 30 ml of fresh ethyl acetate. In this case the extraction proceeded during 1 hour. The ^{196}Au activity was decreased by a factor of 10.

Subsequently, the gold extraction was repeated three times under continuous agitation in the magnetic agitator. In this case the activity of ^{196}Au was decreasing at each cycle by a factor of 5 and that of ^{195m}Pt by a factor of 1.8-2. The loss of a significant amount of ^{195m}Pt at each extraction cycle is caused by its low concentration in the solution, namely, $7\cdot10^{-12}$ mol/l of ^{195m}Pt. The total content of platinum atoms was determined by the yield from the reaction ^{197}Au(γ,n)^{196}Au → ^{196}Pt. In our case the total concentration of platinum atoms in the solution was $6.4\cdot10^{-9}$ mol/l. In total after two extraction cycles we obtained 13 kBq of ^{195m}Pt that was equal to 10% of the initial activity after irradiation in the electron accelerator. In Fig.2 the spectra of ^{195m}Pt solution after final cycle of gold extraction are presented. The number of counts, detected by the Ge(Li)-detector, of the line with 356 keV energy (^{196}Au) makes 1.6% of the number of K-line counts of ^{195m}Pt, that corresponds to 1.9% of the ^{196}Au activity from the ^{195m}Pt activity.

Fig.1. Extractor of gold

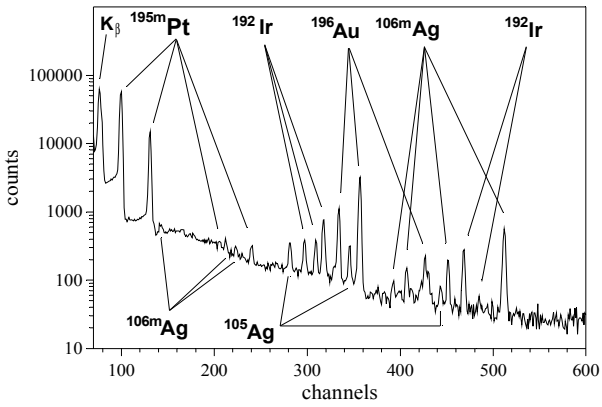

Fig.2. The fragment of the γ-spectrum of the ^{195m}Pt solution after the final extraction cycle

In the spectrum of hydrochloric acid ^{192}Ir takes place which was produced in the reaction ^{197}Au(γ,n α)^{192}Ir. The cross-section of this reaction at a gamma-quantum energy of 30 MeV is less by a factor of 3-5 than that of the reaction ^{197}Au(γ,np)^{195m}Pt. The yield of ^{192}Ir after the final extraction cycle is 50% of the yield of isotope ^{195m}Pt. Proceeding from the above-given data we can conclude that in the hydrochloric acid solution, after finishing all the extraction cycles, the residue of ^{192}Ir was about 10%. Note, that its initial concentration in the solution was $4\text{-}6\cdot10^{-12}$ mol/l. In addition, in the spectrum of Fig.2 one can see a considerable amount of isotopes ^{106m}Ag and ^{105}Ag from the reactions ^{107}Ag(γ ,n)^{106m}Ag and ^{107}Ag(γ,2n)^{105}Ag, which are realized in the silver impurities in gold.

In the practice of commercial ^{195m}Pt production by the reaction ^{197}Au(γ,np)^{195m}Pt the concentration of ^{195m}Pt in the solution will be higher by a factor of 100-200. Therefore, the number of cycles of gold extraction from the solution will be less, respectively, the remaining fraction of the isotope ^{195m}Pt in the solution will be larg-

er. The expected value may be 60…80%. It should be noted that after the final extraction cycle there is $2\cdot10^{-7}$ mol/l in the solution. We suppose that further improvement of the gold extraction technique will allow one to decrease the gold concentration after the final extraction cycle down to 10^{-9} mol/l.

In addition, note that the recrystallization of the obtained radioactive cisplatin will allow one to decrease considerably the gold content in the final product.

The peculiarity of the radioactive cisplatin synthesis in our case is a small quantity of ^{195m}Pt (25 ng). The solution of platinum in the hydrochlorid acid was repeatedly (3-4 times) evaporated on the water bath to obtain a yellow precipitate. The dry precipitate $H_2[PtCl_6]\cdot6\ H_2O$ was subjected to treatment with boiling water and was evaporated again on the water bath [6,7]. Then the fresh 25% solution of potassium chloride was added to the tenfold-water solution of platinum hydrochloric acid up to the complete precipitation.

$$H_2[PtCl_6] + 2KCl = K_2[PtCl_6] = 2HCl\ . \qquad (1)$$

The yellow crystalline precipitation was obtained. After cooling the precipitate was washed during 1.5… 2 hours with the diluted potassium chloride solution and alcohol. The compound is crystallized in the form of yellow octahedrons. The obtained precipitate in the 6-7 fold quantity of water was slowly heated to boiling. In the process, as the quantity was small, water was added to the required volume. A 5% excess of lemon salt (0.39 g $K_2C_2O_4\cdot H_2O$ на 1 g $K_2[PtCl_6]$) was added to the boiling mixture.

$$K_2[PtCl_6]+K_2C_2O_4=K_2[PtCl_4]+2KCl + 2CO_2\ . \qquad (2)$$

Boiling of the solution during 1 hour does not resulted in the formation of red-crimson precipitate. Therefore once more portion of $K_2C_2O_4$ was added. After boiling during 1 hour the red-crimson precipitate was formed. The obtained solution of potassium chloroplatinite $K_2[PtCl_4]$ with addition of a necessary quantity of 20% solution of ammonium acetate (CH_3COONH_4) and potassium chloride was boiled during 1.5 hours with water replenishment. After cooling the precipitate of Pejrone salt of canary color was precipitated.

$$K_2[PtCl_4] + 2CH_3COONH_4 = (NH_3Cl)_2Pt + 2CH_3COOK + 2HCl\ . \qquad (3)$$

3. BIOLOGICAL TESTS

The response of tumor cells on the action of initial and radioactive cisplatin can reflect their sensitility to the chemicals action and to the radiation effect that is very important in the case of antitumor therapy of patients.

Experiments were carried out to investigate the influence of initial and radioactive cisplatin on the Ehrlich adenocarcinoma cells. The cell concentration was $1.8\cdot10^6$cells/ml. The cell vitality was 98%. The estimation of the Ehrlich adenocarcinoma cell vitality after staining with trypan blue was made using the light microscopy in dynamics in 1, 2, 4, 6, 12, 18, 24 and 48 hours. The cells were counted in the Goryaev chamber under the microscope MBB-1 (x900).

The introduced dose of initial cisplatin was 7.5μg/ml, of radioactive cisplatin – 0.017 pg/ml and 0.17 pg/ml [7]. We introduced into every sample 0.03 ml penicillin that corresponded to 180 units, and 0.03 ml streptomycin that corresponded to 300 μg. The samples were stayed in the thermostat at a temperature of 37° for incubation.

The size of tumor cells was measured on the polarization microscope (x200) before cytostatic introduction. The cell size was 0.015 mm. After incubation during 12 hours the cell size was 0.010…0.015 mm with initial cisplatin and 0.005…0.007 mm with radioactive cisplatin.

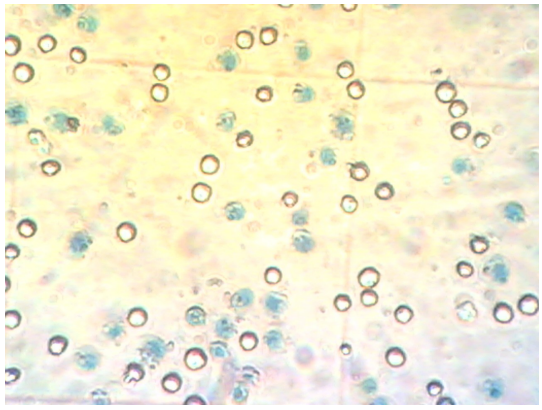

Fig.3. Effect of high-active cisplatin on the Ehrlich cells, 60 min, 0.017 picograms

Fig.3 demonstrates the vital and dead Ehrlich adenocarcinoma cells treated with radioactive cisplatin in dose of 0.017 picograms after incubation during 60 minutes. In the field of vision one can see the vital (unstained) cells and dead (stained with blue) cells. It should be noted that after the radioactive cisplatin action in dose of 0.017 picograms during 1 hour the number of vital cells slightly exceeds the number of dead cells.

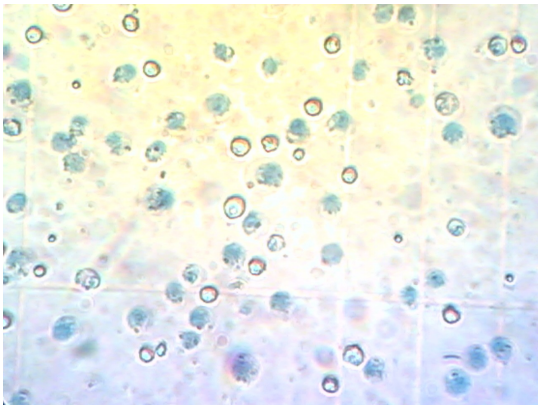

Fig.4. Effect of high-active cisplatin on the Ehrlich cells, 120 min, 0.017 picograms

Fig.4 shows the vital and dead Ehrlich adenocarcinoma cells after introduction of cisplatin in dose of 0.017 picograms and incubation during 2 hours. It is seen that in the field of vision the number of dead

cells is significantly larger relatively to the number of vital cells.

Fig.5 presents the picture of Ehrlich tumor cells after action of radioactive cisplatin in dose of 0.17 picograms. One can see that already under radioactive cisplatin action during 1hour in such dose almost all the cells are dead. The rest vital cells coalesce in coarse conglomerates. Most of them are deformed. A lysis state of cells is observed. Also, as a result of the cell membrane damage the cytoplasm escape into the intercellular space. Thus the rest vital cells lost their capability to divide.

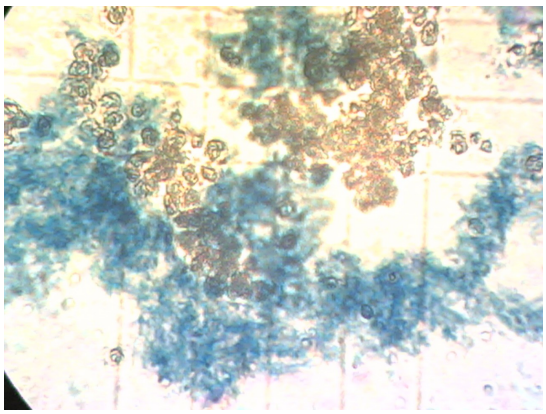

Fig.5. Effect of high-active cisplatin on the Ehrlich cells, 60 min, 0.17 picograms

After action of radioactive cisplatin in dose of 0.017 picograms during 6 and 12 hours in the field of vision we observed solitary cells in the state of pyknosis, as well as, deformed cells, sometimes, of a giant size. The presence of giant cells and normal cells simultaneously evidences on the probability that in future the cells will coalesce in conglomerates. The fact that the cell proliferation decreases is confirmed by investigation dynamics where the inverse relationship between the cell volume increasing and their number in the conglomerate is observed.

Apoptotic bodies were revealed in 18 and 24 hours. A feature of cell apoptosis morphology consists in the appearance of a great number of small-size apoptotic bodies among many dead and vital cells.

After radioactive cisplatin action during 24 hours it is seen that the giant cells disappear, likely, they are dying. One of possible mechanisms of cell death may be the cell inability to withstand the osmotic pressure or to stand against the mechanical force, for example, to the squeeze in the instant of conglomerate formation [8].

Experiments showed that during the first hours of incubation there was not a total death of cells under the action of both the initial and radioactive cisplatin in dose of 0.017 picograms. It means that the cells have different resistance and sensitivity to the action of such factors as radiation and pharmaceutics.

Investigation of the dose effect (cisplatin concentration from 0.01 to 0.17 picogram) on the tumor cell vitality has shown that the increase of radioactive cisplatin dose leads to the higher content of cells with changes typical for necrosis. In the case of necrosis the changes may be in the form of pyknosis and lysis. The cell swelling and distinct destructive changes attract attention. Then the cell membrane is damaged and the cytoplasm contents spreads into the intercellular space. Examination shows that at doses of radioactive cisplatin of 0.17 picograms in the field of vision a great number of cells are in the state of apoptosis. The morphological apoptosis leads to the cell volume decreasing, cell shrinkage and apoptotic corpuscles formation. Apoptotic corpuscles in the form of spherical formations are easily identified. They can be revealed in groups. If they are lonely, in this case they are surrounded light aureole.

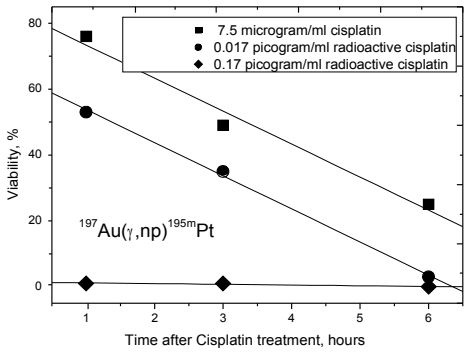

Fig.6. Action of initial and radioactive cisplatin on the Ehrlich adenocarcinoma cell vitality

Fig.6 shows the Ehrlich adenocarcinoma cell vitality after introduction of initial and radioactive cisplatin obtained from the radioactive gold target and subsequently synthesized. As is seen from the figure the Ehrlich adenocarcinoma cell vitality under the initial cisplatin action decreases from 78% after 1 hour to 25% after 6 hours of incubation. Under action of radioactive cisplatin in dose of 0.017 picograms a similar dependence is observed. The vitality of tumor cells under action of radioactive cisplatin during 1hour is 54% and after 6 hours it is 3%. It should be noted that during a short period after introduction of radioactive cisplatin in dose of 0.17 picograms the certainly irreversible tumor cell inhibition takes place. In the dynamics of investigations the cells reveal the loss of potency for the unlimited reproduction, may be even with a short-time retaining of the morphological continuity. One can see that in the initial incubation period (2-6 hours) the number of vital cells with radioactive cisplatin is less than that of those with initial cisplatin. Later we observed a significant difference in decreasing the number of vital cells under action of radioactive cisplatin relatively to the initial cisplatin.

The doses of radioactive cisplatin absorbed by different organs of animals were measured. The cisplatin molecule containing ^{195m}Pt may have an important therapeutic application. Therefore, it is necessary to have an information and reliable estimate of absorbed doses for different organs and tissues in order to perform the fur-

ther calculation of effective doses for patients, which will be treated with cisplatin containing ^{195m}Pt.

The experiment was carried out on animals (white mice, males, weight of 18 g). Radioactive cisplatin in dose of 13 kBq was intraperitoneally injected into the animals. After injection of radioactive and synthesized cisplatin all the animals were living. The absorption dose (mGy/MBq) from ^{195}Pt was measured in different organs (kidney, liver, spleen, bowels, seminal glands, urinary bladder wall, skin). The controlled organs from 10 animals were weighted and placed in the aluminum container installed on the Ge(Li)-detector for the absorbed dose recording. The data obtained have shown that the highest absorption dose of ^{195m}Pt-cisplatin is recorded in the liver (0.72±0.23); kidney (0.40±0.07); seminal glands (0.55±0.15); spleen (0.35±0.05); urinary bladder wall (0.25±0.02); skin (0.21±0.04).

CONCLUSIONS

1.Irradiation of cisplatin pharmaceuticals in the electron accelerator was carried out. Optimum conditions for cisplatin irradiation were determined to reach a maximum specific activity of ^{193m,195m}Pt. The specific activity of radioactive cisplatin equal to 250-100 Bq/mg was obtained.

2.Optimum conditions for gold irradiation in the electron accelerator for ^{195m}Pt production were determined.

3.The method of gold extraction for ^{195m}Pt production was developed.

4.The effect of initial and radioactive cisplatin with a high specific activity (~1Ci/mg) on the suspension of Ehrlich adenocarcinoma cells was investigated. The change of cell morphology depending on the dose of initial and radioactive cisplatin was observed.

5.Necrosis and apoptosis processes leading to the death of cells are revealed under action of radioactive cisplatin in dose of 0.017 picogram/ml, which is less in 10^7 times then the introduced dose of initial cisplatin.

6.The dose of absorption (mGy/MBq) from ^{195m}Pt was measured in different organs (kidney, liver, spleen, bowels, seminal glands, urinary bladder wall, skin). The data obtained have shown that the highest absorption dose of ^{195m}Pt-cisplatin is recorded in the liver, kidney, seminal glands, spleen, urinary bladder wall, skin.

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ОЦЕНКА ПОГЛОЩЕННЫХ ДОЗ СИНТЕЗИРОВАННОГО ЦИСПЛАТИНА НА ОСНОВЕ ^{195m}Pt В РАЗЛИЧНЫХ ОРГАНАХ ЖИВОТНЫХ

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Проведены эксперименты по выделению изотопа платины ^{195m}Pt в реакции ^{197}Au(γ,np)^{195m}Pt на линейном ускорителе электронов для энергии 40 МэВ при токе 10 мкА. Разработана технология выделения ^{195m}Pt из мишени золота в экстракторе типа Кучера-Штоля. Следующий этап технологии заключался в получении синтетического цисплатина на основе ^{195m}Pt. Примесь ^{196}Au в синтезированном цисплатине составила 1,4% от активности ^{195m}Pt. Измерены эффективные дозы поглощения на единицу активности от ^{195m}Pt в различных органах животных, которым был введен радиоактивный цисплатин в дозе 13 кБк. Показано, что дозы поглощения от ^{195m}Pt для различных органов составляли от 0,72 до 0,20 мГр/МБк.

ОЦІНКА ПОГЛИНЕНИХ ДОЗ СИНТЕЗОВАНОГО ЦИСПЛАТИНУ НА ОСНОВІ ^{195m}Pt У РІЗНИХ ОРГАНАХ ТВАРИН

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Проведено експерименти по виділенню ізотопу платини ^{195m}Pt у реакції ^{197}Au(γ,np)^{195m}Pt на лінійному прискорювачі електронів з енергією 40 МеВ і струмом 10 мкА. Розроблено технологію виділення ^{195m}Pt з мішені золота в екстракторі типу Кучера-Штоля. Одержано синтетичний цисплатин на основі ^{195m}Pt. Домішка ^{196}Au у синтезованому цисплатину склала 1,4% від активності ^{195m}Pt. Виміряні ефективні дози поглинання на одиницю активності від ^{195m}Pt у різних органах тварин, яким був уведений радіоактивний цисплатин у дозі 13 кБк. Показано, що дози поглинання ^{195m}Pt цисплатина для різних органів становили від 0,72 до 0,20 мГр/МБк.