Київський національний університет імені Тараса Шевченка
Навчально-науковий центр радіаційної безпеки Київського національного університету імені Тараса Шевченка
Всеукраїнське об'єднання медичних фізиків та інженерів

Медична фізика – сучасний стан, проблеми, шляхи розвитку. Новітні технології

Матеріали IX Міжнародної конференції
(Київ, 23–25 вересня, 2020 рік)

Medical Physics – the Current Status, Problems, the Way of Development. Innovation Technologies

Proceedings of IX International Conference
(Kyiv, September 23–25, 2020)

Київ
2020

УДК 61:53:005.745

Матеріали IX Міжнародної конференції «Медична фізика – сучасний стан, проблеми, шляхи розвитку. Новітні технології» відображають наукові, методичні та практичні результати досліджень, спрямованих на вдосконалення шляхів розвитку медичної фізики, подальшого просування новітніх технологій на ринку медичних послуг.

Конференція проводиться за ініціативою Навчально-наукового центру радіаційної безпеки Київського національного університету імені Тараса Шевченка, Всеукраїнського об'єднання медичних фізиків та інженерів за участю фахівців із провідних закладів вищої освіти, медичних, наукових та регулювальних установ, а також представників МАГАТЕ, Міністерства охорони здоров'я, Академії медичних наук України тощо.

Мета конференції – об'єднати зусилля спільноти в галузі освіти, науки, охорони здоров'я та ядерного регулювання для ефективної підготовки фахівців із медичної фізики.

Proceedings of IX International Conference «Medical physics – the current status, problems, the way of development. Innovation technologies» are reflecting the scientific, methodical and practical results of scientific researches. Results are directed to improve the way of medical physics development in post-Soviet countries and further promotion of innovation technologies in the market of medical services.

The workshop is held by initiative of Taras Shevchenko National University of Kyiv and Ukrainian Association of Medical Physicists and Engineers with the participation of specialists of leading institutions of higher education, medical and scientific organizations, authorities and also representatives of IAEA, Ministry of Public Health of Ukraine, National Academy of Medical Science of Ukraine, etc.

The conference aim is cooperation of community in the area of enlightenment, science, public health and nuclear regulation for effective training of specialists in medical physics.

ISBN 978-617-7288-21-2

©Київський національний університет імені Тараса Шевченка, 2020

4. Кечкер М.И. Руководство по клинической электрокардиографии. – М., 2000. – 395 с.
5. О.Л. Коренівська, Ю.О. Лазебник. Розгляд електрогенезу серцевої діяльності за допомогою створення індуктивно-ємнісної моделі серця. - Вісник ЖДТУ № 4 (31). – 32 с.

PRE-IRRADIATION OF A SOLVENT – A WAY TO RESPECT THE THERAPEUTIC EFFCACY OF SOME WATER- SOLUBLE DRUGS

M.A. Zabolotnyy[1], G.I. Dovbeshko[2], V.E. Orel[3], G.I. Solyanik[4], L.N. Kirkilevskaya[5]

[1] *Taras Shevchenko National University of Kyiv, Ukraine*
[2] *Institute of Physics of NASU, Kyiv, Ukraine*
[3] *National Cancer Institute, Kyiv, Ukraine*
[4] *Institute of Experimental Pathology, Oncology and Radiobiology of NASU, Kyiv, Ukraine*
[5] *Kyiv Medical University, Kyiv, Ukraine*, +380445213284, radbez@gmail.com

Annotation. The work is devoted to the study of the processes that determine the possibilities of the method of increasing the effectiveness of the antitumor action of already known antitumor drugs without the use of foreign nano dipurities using high-energy electron irradiation. The electron energy was 2 MeV. The method is based on the use of the original technique, which uses irradiation of the solvent (water or saline) before the introduction of a drug (doxorubicin). Conformational changes in doxorubicin molecules in irradiated saline were analysed by changes in their vibrational spectra, which were recorded using an IR-Fourier spectrometer. Quantum chemical calculations were performed using the Gaussian program, the method of density functional (B3LYP). The geometry of the doxorubicin molecule was optimized and its oscillation spectrum was calculated. To study the pharmacological activity of the antitumor drug doxorubicin used Lewis lung carcinoma. Cells were maintained in RPMI 1640 medium with the addition of 10% ETS, 2 mm L-glutamine and 40 μg / ml gentamicin at 37 ° C. Studies have shown that the use of pre-irradiated saline (0.9% NaCl) for the antitumor drug doxorubicin significantly alters the conformational properties of its molecules. The minimum dose of high-energy electron irradiation (2

MeV) absorbed by the solvent, at which changes in the conformation states of the drugs dissolved in them are recorded, is equal to 4 kGy.

Key words: irradiation, conformation, electrons, molecule, konium, doxorubicin.

Introduction. Experience with antitumor chemotherapy has shown its limited capabilities and low efficacy in the treatment of locally advanced and disseminated forms of malignant neoplasms. In this regard, the definition of new biologically active materials, the study of their physical, chemical and therapeutic properties and the creation on their basis of effective and low - toxic antitumor drugs is one of the most pressing tasks of modern pharmacology and practical oncology [1, 2, 3] an important issue is the choice of the optimal modifier of therapeutic drugs, which is usually in a nanostructured state. Note that the modification of drug molecules by nanosized particles has important theoretical and practical significance, as it provides the opportunity to obtain biocompatibility with cells of the body, specific interaction with living tissues. Preliminary studies have shown the prospects of a new non-destructive method of modifying both the physical and therapeutic properties of some antitumor drugs without changing their chemical composition.

The aim of the work is to study the regularity of the method of increasing the effectiveness of antitumor action of already known antitumor drugs without the use of foreign nanodipurities using high-energy electron irradiation, to reduce the dose of antitumor drugs and minimize side effects when used in oncology.

Experemental procedure. The studies used saline 0.9% NaCl (Novopharm-Biosynthesis, Ukraine). Saline, collected in sterile medical syringes of 20 ml, was irradiated with electrons with an energy of 2.0 MeV using a linear accelerator ILU-6. The dose of absorbed radiation ranged from 4 to 80 kGy. Under such electron irradiation, the solvent temperature changed by no more than 5 C^0. Characteristics of the electron irradiation process of doxorubicin solutions are given in Table 1.

Table. 1.

Position of points of local maxima of absorption spectra

Fluence of the electron flux, sm^{-2}	Irradiation time s	Absorbed dose of irradiation, kGy
4×10^{13}	45 c	5
6×10^{13}	60 c	10
1×10^{14}	76c	20
2×10^{14}	270	35
4×10^{14}	520	70
4×10^{14}	580	80

Solutions of doxorubicin (adriblastine) were prepared using Actavik Italy powder, SpA and saline, bringing the concentration of the active drug to 5 mg / ml and and Conium (Weleda, Germany). Drug Conium, contains a number of alkaloids, the main of which are Coniin ($C_8H_{17}N$), N-Methylconiin ($C_9H_{19}N$), γ- Konitsiin ($C_8H_{15}N$), Conhydrin ($C_8H_{17}NO$) and Pseudoconhydrin ($C_8H_{17}NO$).

Conformational changes in doxorubicin molecules in irradiated saline were analysed for changes in their vibrational spectra, which were recorded using an IR-Fourier spectrometer (Bruker IFS 66, Germany) and a Shimadzu UV-260 diffuse knockout spectrophotometer. The accuracy of determining the wave number was 0.2 cm-1, and the accuracy of determining the transmission - 0.1%. Processing of IR spectra was performed using the program OPUS 5.5. Measurements were performed no later than 10 days after irradiation of saline. The temperature of the sample was in the range of 20–25 C^0.

Quantum chemical studies used the GAUSSIAN program, which was used to calculate the vibrational frequencies of the doxorubicin molecule in vacuum and water.

Results and discution. The results of measurements in the visible and IR regions of the spectra are illustrated by the graphs

presented in Figs. 1 and Fig.2, respectively. The time between irradiation of the samples and registration of their vibrational spectra did not exceed 14–23 days. The measurements showed that the absorption of the samples in this case was constant. The results of the measurements in the visible region of the spectrum are illustrated in Fig. 1, which shows the spectral dependences of the absorption of doxorubicin molecules in unirradiated and irradiated (70 kGy) saline.

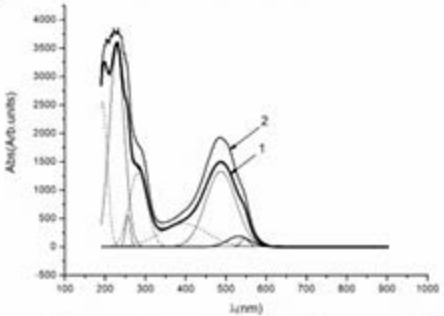


Fig. 1. Absorption spectra in the visible region of a doxorubicin solution dissolved in saline solution not irradiated (curve 1) and pre-irradiated (curve 2)

The absorption spectrum of the solution obtained without prior irradiation was analysed using its representation as a composition of Gaussian functions. The graph of the sum of these Gaussian functions conveys all the characteristic features of the experimentally established spectrum (Pearson's pairwise correlation coefficient between them is 0.98). The absorption of radiation in these regions is associated with the excitation of electrons of the s-, p-and n-orbitals of the ground state and the transitions of molecules into the excited state. Therefore, studying the shift of the positions of the maxima and the change in intensity in this area, we can draw conclusions about the change in the optical properties of the doxorubicin molecule. The dependence of the positions of the local maxima of the sectors on the value of the

absorbed dose in the optical absorption spectra taken immediately after irradiation of the solvent and the preparation of solutions with doxorubicin are shown in Table 2.

Table 2.

Dependence of the position of the absorption maxima on the dose in the optical absorption spectra taken immediately after irradiation of the solvent and preparation of solutions with doxorubicin

DOX +NaCl, 0 kGy, λ (nm)	193,23	225,86	256,95	280,64	393,33	486,37	530,18	545,21
DOX +NaCl 70 kGy, λ (nm)	192,50	235,11	255,24	291,69	401,87	489,76	529,81	535,42

Significant dependence on the amount of absorbed dose is also shown by the absorption spectra in the IR range, illustrating the data shown in Fig.2.

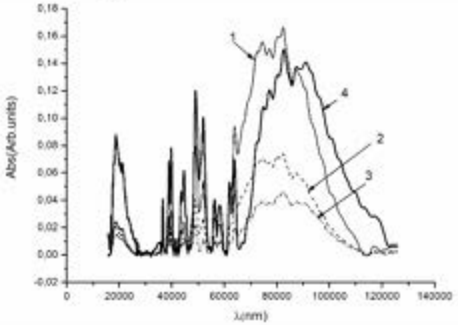


Fig.2. The dependence of the normalized absorption of doxorubicin on the wavelength in the unirradiated and irradiated solution of 0.9% NaCl at different doses of absorbed electron irradiation

Curve 1 presented in Fig.2 describes the absorption spectrum of doxorubicin in non-irradiated saline, curve 2 was obtained about the absorbed dose of 10 kGy, curve 3 - 35 kGy, and 4 - 70 kGy. As can be seen from Fig.2 for the above spectra is characterized by a

significant non-monotonic dependence of the configuration of the spectra (the ratio of the amplitudes of high-frequency and low-frequency maxima) from the absorbed dose. This behavior may be due to coagulation (clustering) of babstones [5], which can be realized at high values of the concentration of babstones (at high levels of radiation).

Studies have shown that the minimum dose of high-energy electron irradiation absorbed by the solvent, at which changes in the conformation states of the drugs dissolved in them are recorded, is 4 kGy. In this case, the radiation-induced changes in the absorption spectra of the samples exceed the noise effects of physiological solutions.

Studies of the ability of high-energy electron irradiation of saline as a drug solvent to modify the pharmacological activity of the antitumor drug doxorubicin were investigated in vitro using the Lewis lung cancer cell line (LLC). Studies have confirmed our previous conclusion [6] that the use of doxorubicin dissolved in irradiated saline leads to increased cytotoxic / cytostatic effects. This potentiating effect is most significant at low concentrations of doxorubicin.

Conclusions.

1. Preliminary irradiation of physiological solution causes a change in the absorption spectra of doxorubicin dissolved in it in the visible and IR region of the spectrum. Changes in the spectra of these spectra are characterized by a significant non-monotonic dependence of the configuration of the spectra (the ratio of the amplitudes of high-frequency and low-frequency maxima) on the absorbed dose.
2. The use of pre-irradiated solvent (0.9% NaCl) antitumor drug doxorubicin significantly changes their conformational properties. The minimum dose of high-energy electron irradiation (2 MeV) absorbed by the solvent, at which changes in the conformation states of the drugs dissolved in them are recorded, is equal to 4 kGy. In this case, the radiation-induced changes in the absorption spectra of the samples exceed the noise effects of physiological solutions.

3. The modifying effect of high-energy electron irradiation of the doxorubicin solvent persists for 2-3 weeks.

4. The structural forms were determined, the values of the dipole moments and the energy of the ground state of alkaloids included in the konium were calculated: koniyina, N-methylconiine, γ-konitsiina, conhydrin and pseudoconhydrin. It has been established that the conformations of the molecules of alkaloids with the lowest energy have the maximum possible linear dimensions and the smallest values (for stable states) of the dipole moment [6].

REFERENCES

1. Ambili Remesh. Toxicities of anticancer drugs and its management// International Journal of Basic and Clinical Pharmacology. – 2012 – Vol.1 – № 1. – P. 2 – 12.

2. V.B. Orel, M.A. Zabolotnyy, V.E. Orel. Heterogeneity of hypoxia in solid tumours and mechanochemical reactions with oxygen nanobubbles// Medical Hypotheses. – 2017 – №102 – P.82-86, doi; 10.1016/j.mehy.2017.03.006.

3. Oncology 2020: a drug development and approval paradigm.// Annals of Oncology – 2020 – №26 – P. 2347 – 2350; 2015 doi:10.1093/annonc/mdv353.

4. М.А. Заболотний, М.П. Куліш, О.П. Дмитренко, Г.І. Соляник, Ю.І. Прилуцький, М.А. Драпіковський, М.О. Кузьменко, Н.А. Полуян, В.А. Кияшко. Спосіб модифікації водорозчинних протипухлинних препаратів за допомогою радіаційного опромінення, Патент на винахід № 116227, Дата подання заявки: 07.07.2015, Зареєстровано 26.02.2018.

5. Fang C-K., Ko H-C., Yang C-W., Lu Y-H., Hwang I-S. Nucleation processes of nanobubbles at a solid/water interface// Scientific Reports – 2016 - №6 (24651) – P.1-10.

6. L.I. Aslamova, M.A. Zabolotnyy, G.I. Dovbeshko, G.I. Solyanik. Electron irradiation as a method of increasing efficacy of some water soluble drugs in oncology// Proceedings of International Conference "Medical Physics 2019 in the Baltic States", 7 – 9 November 2019 – Kaunas – Lithuania – P. 151 – 152.

Медична фізика – сучасний стан, проблеми, шляхи розвитку. Новітні технології

Матеріали IX Міжнародної конференції
(Київ, 23–25 вересня, 2020 рік)

Підписано до друку 25.09.2020
Формат 60x84/16. Ум. друк. арк. 13,49. Тираж 300 прим. Зам 348
Державне підприємство
«Редакція інформаційного бюлетеня
«Офіційний вісник Президента України»
01014, м. Київ, вул. Петра Болбочана, 8, корпус 6
Тел. / факс: 254-51-51

Свідоцтво про внесення
Суб'єкта видавничої справи до державного реєстру
Видавців, виготівників і розповсюджувачів видавничої продукції
ДК № 3862 від 18.02.2010