

Research Article

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Evaluation of absorbed dose in Gadolinium neutron capture therapy

Abstract: Gadolinium neutron capture therapy (GdNCT) is used for treatment of radioresistant malignant tumors. The absorbed dose in GdNCT can be divided into four primary dose components: thermal neutron, fast neutron, photon and natural gadolinium doses. The most significant is the dose created by natural gadolinium. The amount of gadolinium at the irradiated region is changeable and depends on the gadolinium delivery agent and on the structure of the location where the agent is injected. To define the time dependence of the gadolinium concentration $\rho(t)$ in the irradiated region the pharmacokinetics of gadolinium delivery agent (Magnevist) was studied at intratumoral injection in mice and intramuscular injection in rats. A polynomial approximation was applied to the experimental data and the influence of $\rho(t)$ on the relative change of the absorbed dose of gadolinium was studied.

Keywords: GdNCT; Magnevist; absorbed dose; kerma; amount of gadolinium

PACS: 87.56.-V, 87.55.dk

DOI 10.1515/phys-2015-0022

Received June 20, 2014; accepted January 01, 2015

1 Introduction

The aim of radiation therapy is to give an adequate absorbed dose of radiation to the bodies containing malignant cells (the target) whilst minimizing the dose to healthy tissue. Gadolinium neutron capture therapy (GdNCT) is one of perspective to future method of radiation therapy. GdNCT is based on the nuclear capture and other reactions that occur when ^{155}Gd and ^{157}Gd , which are non-radioactive constituents of natural elemen-

tal gadolinium, are irradiated with low energy (0.025 eV) thermal neutrons. These result in the production of high energy gamma-rays, internal conversion electrons, X-rays and Auger electrons. For the development of GdNCT a more concrete characterization of this production from nuclear reactions in ^{155}Gd and ^{157}Gd is required. Uncertainties in physical data for conversion gamma and x - rays, internal conversion and Auger electrons make it impossible to precisely determine radiation absorbed dose in malignant tumors. GdNCT requires the development of Gd delivery agents to tumor. Gd-DTPA (Diethylenetriaminepentaacetic acid) is presently available and has a very high tumor-to-tissue uptake ratio [1, 2]. In vitro experiments can provide mass concentrations growth to 1000 ppm Gd in tumor cells. In prior cancer research work [3], it was suggested that it can possibly enter the nucleus of cell. Therefore, more investigation is needed to determine if Gd-DTPA or other Gd delivery agents selectively enter a cell's nucleus. To determine absorbed dose it is also important to study the time-dependence of Gd-DTPA in tumors and organs. High concentrations or the long retention time of the Gd compounds in organs may result in high organ radiation doses. Additionally, high concentrations of Gd compounds in organs located near the brain, such as the thyroid, may influence treatment planning for GdNCT because exposure to a low flux of thermal neutrons will increase dose to those organs. The neutron irradiation facility for development of the neutron capture therapy (NCT) method at the horizontal channel of the WWR-SM research reactor of the Institute of Nuclear Physics Uzbek Academy of Science (INP UzAS) has been created [4]. Magnevist (Gd-DTPA) has been selected as the gadolinium delivery agent for the further research on GdNCT. This article describes the research conducted in INP UzAS dedicated to cancer treatment using this preparation. Based on a prompt and convenient method for radiographic visualization of gadolinium-containing preparation [5] the Magnevist pharmacokinetics was studied at the intratumoral injection in mice and intramuscular injection in rats. The data obtained allowed for the semiquantitative estimation of the amount of gadolinium in the injection site. The amount of Magnevist measured in the irradiated

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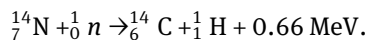
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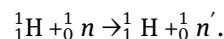
region over time is used for the correct definition of absorbed dose.

2 Absorbed Doses in GdNCT

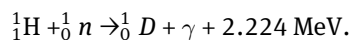
Radiation delivered in NCT is a complex of mixed fields of high and low LET radiation. It depends on the spatial, spectral and angular characteristics of the incident neutron beam as well as the geometry and elemental composition of the target. The absorbed dose in gadolinium neutron capture therapy (GdNCT) can be divided into four primary dose components: thermal neutron, fast neutron, photon and natural gadolinium dose. The thermal neutron dose primarily arises from the thermal neutron capture reaction in ^{14}N :



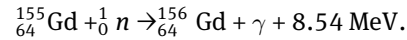
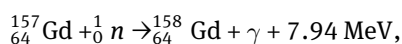
It comprises 96% of the neutron kerma of ICRU 46 brain tissue samples [7] below 0.5 eV energy cutoff for thermal neutrons. The fast neutron dose can be formed primarily due to elastic neutron collisions with hydrogen:



It represents 90% of the adult brain kerma between energies 600 eV and 3 MeV. Other neutron reactions, primarily with ^{12}C , ^{16}O and ^{31}P contribute 4-8% to the brain kerma between ~ 40 eV and 5 MeV, but certain resonance energies contribute more. The photon dose components originate from two sources, contaminating photons in the neutron beam incident on the target and prompt gammas produced by neutron capture reactions in the target, and are represented by:



Natural Gd has 7 stable isotopes including ^{152}Gd (0.205%), ^{154}Gd (2.23%), ^{155}Gd (15.10%), ^{156}Gd (20.60%), ^{157}Gd (15.70%), ^{158}Gd (24.50%), ^{160}Gd (21.60%). Among them, ^{155}Gd and ^{157}Gd have the most excellent neutron capture properties with thermal neutron capture cross-sections of 60800 and 255000 barns respectively and which is approximately 16 and 66 times that of ^{10}B . The nuclear reaction cross sections for the other isotopes are negligibly small for dose calculations. Therefore, we consider nuclear reactions with these isotopes making the major contribution to the summary dose (20% ^{155}Gd and 80% ^{157}Gd) from ^{nat}Gd :



In these reactions, except for high-energy γ -rays, internal conversion electrons, X-rays and Auger electrons are produced.

According to [6] in γ -rays ranging in energy from 0.079 MeV to 7.88 MeV the energy of internal conversion electrons is 45-66 keV, Auger electrons 5-9 keV and X-rays ~ 10.7 -38.4 keV at neutron capture reaction in ^{157}Gd . At present, exact estimations of these types of radiation do not exist. The available data is inconclusive [7?–14].

Exact measurement of the absorbed dose in biological tissues is a difficult experimental problem. Problems of neutron radiation dosimetry are related to the sensitivity of devices. Sensitivity of almost all dosimeters depends on energy of neutrons. Therefore, for an estimation of the absorbed dose definition using kerma K – as a close analogue of the absorbed dose is convenient. At the equilibrium of the secondary charged particles kerma will be equal to the absorbed dose. The advantage of kerma is that it can be calculated both for a known monoenergetic neutron flux, and for a spectrum of neutrons. When the kerma is calculated all processes forming the absorbed dose in a biological tissues are taken into account. By using the values of partial components of the dose rate in soft biological tissue it is possible to calculate the value of the total absorbed dose rate depending on the ^{nat}Gd concentration (ρ_{Gds}) in the tissue:

$$D_{\text{total}} = D_n + D_\gamma + \rho_{\text{ppm Gd}}(D_n^{1 \text{ ppm Gd}} + D_\gamma^{1 \text{ ppm Gd}}). \quad (1)$$

This formula can be written as follows:

$$K_{\text{total}} = K_n + K_\gamma + \rho_{\text{Gd}}(k_n^{1 \text{ ppm Gd}} + k_\gamma^{1 \text{ ppm Gd}}), \quad (2)$$

where

$$K_n = \int_{E_n^{\text{min}}}^{E_n^{\text{max}}} k(E_n) \Phi(E_n) dE_n, \quad (3)$$

$$K_\gamma = \int_{E_\gamma^{\text{min}}}^{E_\gamma^{\text{max}}} k(E_\gamma) \Phi(E_\gamma) dE_\gamma, \quad (4)$$

where $k(E_n)$ – is the energy dependence of specific partial kerma of nuclide calculated for different nuclides of irradiated targets in the energy range from thermal neutrons up to 100 MeV [16], $\text{Gy cm}^2/\text{neutron}$; $\Phi(E_n)dE$ – the neutron flux in the energy interval dE , $\text{neutron/cm}^2 \times \text{s}$;

$k_n^{1 \text{ ppm Gd}}$ – the energy dependence of specific partial kerma of the nuclide calculated for 1 ppm ^{nat}Gd in neutrons with energy range from 10^{-8} to 20 MeV;

$k_\gamma^{1 \text{ ppm Gd}}$ – the energy dependence of specific partial kerma of the nuclide calculated for 1 ppm ^{nat}Gd in photons with energy range from 10^{-6} to 20 MeV.

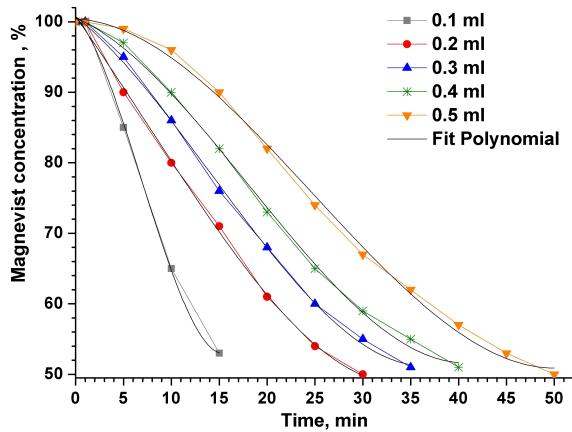


Figure 1: The time dependence of Magnevist concentration at intratumoral injection.

A report on the determination of kerma in biological tissue and for 1 g of natural gadolinium in 1 g of biological tissue irradiated by an epithermal neutron beam in the WWR-SM INP AS RUz was presented in [17]. For 1 g of biological tissue, neutron kerma and photon kerma occur to be $K_n^{bt} = 1.35 \cdot 10^{-4}$ Gy/s and $K_\gamma^{bt} = 6.13 \cdot 10^{-7}$ Gy/s, respectively. For 1 g of natural gadolinium in 1 g of biological tissue the values of kerma occur to be $k_n^{1\text{ppm Gd}} = 3 \cdot 10^{-7}$ Gy/s and $k_\gamma^{1\text{ppm Gd}} = 1.22 \cdot 10^{-10}$ Gy/s, respectively, for a given beam. However, some of our Magnevist pharmacokinetics studies show that in order to take into account the change in gadolinium quantity in the irradiated region, a full kerma expression for biological tissue should be presented as follows:

$$K_{total} = K_n + K_\gamma + \left[k_n^{1\text{ppm Gd}} + k_\gamma^{1\text{ppm Gd}} \right] \int_{t_i}^{t_f} \rho(t) dt, \quad (5)$$

where $\rho(t)$ - the amount of gadolinium in ppm in the irradiated region depending on time, t_i and t_f initial and final irradiation time, respectively.

3 Time dependency of gadolinium amount at intratumoral and intramuscular injections of Magnevist

The preparation Magnevist was designed as a nuclear magnetic resonance-contrast agent for intravenous injection and its pharmacokinetics at such introduction is well known. Pharmacokinetics of various Gd-containing preparations and compounds for NCT was studied by dif-

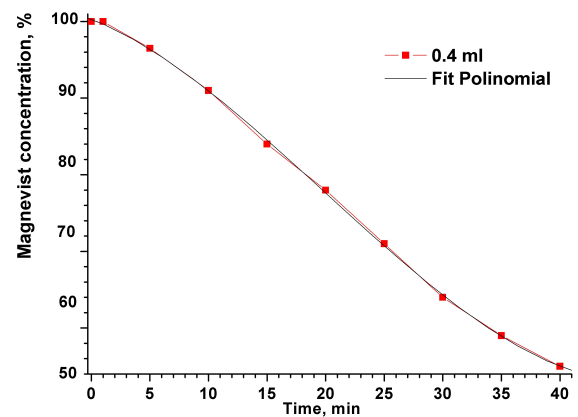


Figure 2: The time dependence of Magnevist concentration at intramuscular injection.

ferent authors [18, 19]. However, pharmacokinetics of Magnevist was poorly investigated for other injection modes, in particular, at intratumoral and intramuscular injections, which were applied in NCT experiments on animals. For a definition of the absorbed dose depending on gadolinium concentration decrease from an irradiated target the pharmacokinetics of Magnevist at intratumoral injection on mice and intramuscular injection on rats was studied. For this purpose a fast and convenient method of Magnevist visualization was developed [16], allowing a semiquantitative estimation of preparation content in an injection location.

For the experiment white male mice and normal healthy white rats were used. To study the pharmacokinetics of Magnevist at intratumoral injection an S180 sarcoma strain was inoculated into the hip of the right rear leg of the mice. The experiment used matured tumours with sizes from 0.5÷1.0 cm to 5.0÷4.0 cm. To study the pharmacokinetics of Magnevist at intramuscular injection 0.4 ml of Magnevist was injected into the right muscle of each rat's hip. Experiments with intramuscular injection were conducted at the same dose of 0.4 ml. Experiment at one dose 0.4 ml is connected with quantity of tested rats. For each dose injection, the groups of 12 mice/rats were used. Roentgenoscopy of the rats and mice was produced on Sirescop Siemens x-ray equipment. Roentgenograms were skiagraphed before injection (control) and at 1, 2.5 and 5 min after injection and then every 5 min until 65 min inclusive after injection. Roentgenograms were processed by means of Image J2x2.1.4.7ud2 software (Wayne Rasband, National Institute of Health, USA). The x-ray contrasting properties of gadolinium-containing preparations [Information leaflet of Optimark preparation of Malinkrodt Inc. company, USA] were used for definition of Magnevist pharmacokinetics. The experimental material

and methods are given in detail in [5]. Here we will concentrate on the received results only. Based on the received data the dependence of Magnevist concentration decrease in a tumour from the injected dose is plotted in Figure 1. The experimental dependence of Magnevist concentration on time for 0.4 ml dose after intramuscular injection in rats is plotted Figure 2. For the analysis of the experimental data polynomial fitting was used. For the experimental dataset for every dose the polynomial fitting formula was $y = b_0 + b_1x + b_2x^2 + b_3x^3$. The same fitting procedure was used for the experimental dataset at the intratumoral and intramuscular injections. The goodness of fit is 98%. The data was processed by means of Origin 8.0.

This analysis shows the dynamics of Magnevist in tumors and muscle. For intratumoral Magnevist injection the optimal concentration of the preparation (80%) remains for 10 - 25 minutes depending on the injected dose. Our data is in good agreement with results obtained for Dipentast, where half-elimination at intratumoral injection to B16 melanoma in mice was 23 ± 5 minutes [14, 15]. This shows Magnevist eliminates out of the tumour sufficiently fast. For intramuscular injection of Magnevist, the optimal concentration of the preparation (to 80%) preserved within 15-20 min. Thus during exposure time the amount of preparation in the irradiation field will significantly change.

4 Evaluation of absorbed dose in GdNCT

The influence of Magnevist dynamics on the change of absorbed dose has been investigated for $\rho = 20315$ ppm of ^{nat}Gd . A change of initial Magnevist concentration during an irradiation time results in the change of ρ with time. We consider that the decrease of gadolinium with time is defined by the decrease of Magnevist from an injection location. Therefore, to define $\rho(t)$ the polynomial fits from the results are used. The results of $\rho(t)$ calculations are presented in Table 1 and 2. It follows from expression (5) that the basic contribution to the absorbed dose gives the amount of gadolinium – $\rho(t)$. Therefore, the dose from gadolinium with the account of $\rho(t)$ has been investigated. For quantitative (in a percentage ratio) estimation of Gd amount dynamics in an injection place we will consider the value:

$$\delta(t) = \frac{|\rho - \rho(t)|}{\rho}, \quad (6)$$

in Tables 1 and 2 value $\delta(t)$ – shows influence of $\rho(t)$ on relative change of the absorbed dose from gadolinium.

Table 1: The influence $\rho(t)$ on relative change of the absorbed dose from gadolinium. Intratumoral injection.

Dose of Magnevist, ml ($\rho = 20315$ ppm of ^{nat}Gd)	t , min	$\rho(t)$, ppm	$\delta(t)$
0.1	5	17175	0.155
	8	14379	0.292
	10	12018	0.408
0.2	15	17548	0.136
	20	16363	0.194
	25	14953	0.264
	30	13264	0.347
0.3	15	18627	0.083
	20	17705	0.128
	25	16546	0.186
	30	15110	0.256
0.4	15	19322	0.049
	20	18786	0.075
	25	18118	0.108
	30	17301	0.148
0.5	15	19774	0.027
	20	19442	0.043
	25	19017	0.064
	30	18489	0.090
	35	17849	0.121

From tables 1 and 2 it is clear that the dynamics of Gd amount in the injection place depends on the injected dose of Gd. Namely, the $\delta(t)$ value decreases with the increase of injected dose of Magnevist (Gd).

5 Conclusion

For GdNCT studies Gd compounds such as Magnevist were used for experiments on biological objects at specialized reactor's horizontal channel. In the preclinical studies on experimental animals the different concentrations of Magnevist were tested. Distributions of Gd in tumors on mice and in muscles on rats were obtained. The dependence of Magnevist concentration in the irradiation place depending on time was experimentally determined. The description of experimental data by polynomial fitting was carried out. Gadolinium amount - $\rho(t)$ in a tumor at irradiation duration and the absorbed dose from gadolinium were calculated. The dynamics of Gd amount in the injection place depends on the injected dose of Gd. With increasing in-

Table 2: The influence $\rho(t)$ on relative change of the absorbed dose from gadolinium. Intramuscular injection.

Dose of Magnevist, ml ($\rho = 20315$ ppm of ^{nat}Gd)	t , min	$\rho(t)$, ppm	$\delta(t)$
0.4	5	17175	0.155
	8	14379	0.292
	10	12018	0.408

jected dose of Magnevist (Gd) the value (t) decreases. The dependence - $\delta(t)$ allows definition of the optimal time of irradiation for different doses of Magnevist. The results are necessary for the correct definition of absorbed dose in GdNCT using Magnevist. These results will be used in experiments on biological objects and in clinical tests of cancer treatment by the GdNCT method.

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