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Медицина є прикладом інтеграції багатьох наук. Наукові дослідження у сучасній медицині на основі досягнень фізики, хімії, біології, інформатики та інших наук відкривають нові можливості для вивчення процесів, які відбуваються в живих організмах, та вимагають якісних змін у підготовці медиків. Науково-практична інтернет-конференція «**Розвиток природничих наук як основа новітніх досягнень у медицині**» покликана змінювати свідомость людей, характер їхньої діяльності та стимулювати зміни у підготовці медичних кадрів. Вміле застосування сучасних природничо-наукових досягнень є запорукою подальшого розвитку медицини як галузі знань.

Конференція присвячена висвітленню нових теоретичних і прикладних результатів у галузі природничих наук та інформаційних технологій, що є важливими для розвитку медицини та стимулювання взаємодії між науковцями природничих та медичних наук.

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У збірнику подані матеріали науково-практичної інтернет-конференції «Розвиток природничих наук як основа новітніх досягнень у медицині». У статтях та тезах представлені результати теоретичних і експериментальних досліджень.

Матеріали подаються в авторській редакції. Відповідальність за достовірність інформації, правильність фактів, цитат та посилань несуть автори.

Для наукових та науково-педагогічних співробітників, викладачів закладів вищої освіти, аспірантів та студентів.

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A mathematical model of transport kinetics of 99mTc radiotracers. an intravenous administration

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Abstract. The proposed four-compartment mathematical model describes transport kinetics of 99m-technetium radiotracers at intravenous administration process with taking into account radiopharmaceutical accumulation, elimination and radioactive decay. The dependencies of the tracer concentration versus the time are analyzed. The obtained data can be used to determine the transport coefficients. The model can be used for individual transport parameter calculation at administration of diagnostic/therapeutic dose loads.

Key words: Transport kinetics of radiotracers, circulatory system, lymphatic system, mathematical model.

The term “radiopharmaceutical” denotes the association of a radionuclide and pharmaceutical, i.e. symbiosis of biological, chemical and physical properties. Radiopharmaceuticals are approved for use in humans for diagnostic purposes chemical compounds whose molecules contain radionuclides. The method of diagnostics or radionuclide study of morphological and functional condition of the body using radionuclides or radionuclide-labeled indicators is one of the most common methods of detecting cancer. Radiopharmaceuticals are selected with consideration of its radiopharmaceutical dynamic and nuclear-physical properties. Dynamics of radiopharmaceuticals is defined by a chemical compound that is the basis for radiopharmaceutical preparation. Registration of radiopharmaceutical is determined by the type of decay of the nuclide, by which it is marked. Some radiopharmaceuticals are called “radiotracers” because they are used only to diagnose (“trace”) dysfunctions in body tissues [1]. A radiopharmaceutical introduced into the body is firstly uniformly distributed in the blood [2], and then selectively trapped by certain organs and tissues. Radiopharmaceuticals selectively accumulating in tumor tissues are called the tumor-imaging agents. They are mainly included in cells with a high mitotic and metabolic activity. Due to high concentration of radiopharmaceuticals a tumor area will emerge on a scintigram – the graphic record obtained by scintigraphy – as a hot site. Areas with increased accumulation of a radiotracer are called hot areas; usually they correspond to overactive functioning body areas - areas of hyperplasia, some types of tumors, inflammatory tissue changes [3-4]. Radiopharmaceutical choice is caused by its

pharmaceutical peculiarities and depends on tumor localization [3]. Radiopharmaceuticals are used in nuclear medicine as tracers for diagnostics and therapy of many diseases. Technetium 99m (^{99m}Tc) serves as gamma-rays-emitting tracer nuclide for many radiopharmaceuticals. More than 30 different ^{99m}Tc based radiopharmaceuticals are known, which are used for imaging and functional studies in various organs.

Radiotracer dynamics are caused by different ways of radiotracer administration (intravenous, intradermal/subcutaneous, intratumoral, intraperitoneal). In the case of intravenous administration radiotracers are captured by the blood vessel, then depending on the size they move to the interstitium [6] and into the lymphatic system and are trapped by a sentinel lymph node (SLN) of the lymphatic system. The size of a radiotracer is an essential parameter. If a size of a radiotracer is less than 4-5 nm, it penetrates capillary membranes without retention in SLN, if a radiotracer size is 100-200 nm, it penetrates fast in SLN.

The interstitium or the interstitial space is a contiguous fluid-filled space existing between a structural barrier, such as a cell wall or the skin, and internal structures, such as organs, including muscles and the circulatory system [6]. The fluid in this space is called interstitial fluid, comprises water and solutes, and drains into the lymph system. The interstitial compartment is composed of connective and supporting tissues within the body – called the extracellular matrix – that are situated outside the blood and lymphatic vessels and the parenchyma of organs. The interstitium/interstitial space is similar in all tissues. The structure and elements of the interstitial space are described in details in [5]. Entry of extracellular fluid and protein into the initial lymphatic vessel occurs through interendothelial openings and by vesicular transport through the endothelial cells. Interendothelial openings may allow cells (macrophages, lymphocytes, erythrocytes) and cellular debris to directly enter lymphatic vessels. Mechanisms of particle transport into/inside of the lymphatic vessels are reviewed in [5]. Role of a particle size is very important.

Most radionuclide lymphatic flow studies use different agents: 99mTc-sulfur colloids, 99mTc-nano- and microaggregated albumin, 99mTc-antimonysulfide, 99mTc – phytate, colloidal gold particles, liposomes, and emulsions administered into the interstitial space of animals and humans. Particles smaller than a few nanometers usually leak into blood capillaries whereas larger particles (up to about 100 nm) can enter the lymphatic capillaries and be transported to lymph nodes.

Mathematical model of radiotracer transport kinetics

A correct mathematical model of radiotracer dynamics has to take into account a very complicated anatomical structure of an organism and different physiological/ pathologic(al) processes, as well as physical and chemical processes, namely diffusion, accumulation, elimination

and radioactive decay of radiotracers. After bolus intravenous administration of the radiotracers the process of transferring the radiotracers by blood vessels is begun and the so-called radiotracer "dilution" process is realized, namely the absorption of radiotracers by other organs and tissues and radiotracer decay. The part of radiopharmaceuticals which is absorbed by cells is immediately metabolized, and metabolic products quickly returned to the general blood circulation. The processes taken into account in the model are the following ones: 1) radioactive decay of pharmaceuticals; 2) accumulation of pharmaceuticals in the interstitium; 3) accumulation of pharmaceuticals in the lymphatic system; 4) transport of pharmaceuticals from the blood vessels; 5) transport of pharmaceuticals and metabolites from the interstitium in the blood vessels, 6) transport of pharmaceuticals from the lymphatic system to the blood vessels.

The model of transport kinetics of radiotracers is described by a system of differential equations of the 1st order for radiotracer concentration levels in the blood-vascular system, in the interstitium, in the lymphatic system and in the urinary system. The system of equations describes the processes of accumulation/retention of radiotracers in the cells, the radiotracer elimination/washout, and radiotracer radioactive decay. This system is similar to four-compartment models, where the amount of radiotracers in each compartment is proportional to the radiotracer concentration:

$$\begin{cases} \dfrac{dx}{dt} = -\lambda x(t) - \beta_{xw} x(t) + \beta_{zx} z(t) \\ \dfrac{dz}{dt} = -\lambda z(t) - (\beta_{zx} + \beta_{zu}) z(t) + \beta_{wz} w(t) \\ \dfrac{dw}{dt} = -\lambda w(t) - \beta_{wz} w(t) + \beta_{xw} x(t) \\ \dfrac{du}{dt} = -\lambda u(t) + \beta_{zu} z(t) \end{cases}, \quad (1)$$

where λ is the radioactive decay constant of radiotracers, $x(t)$ is the concentration of radiotracers in the interstitium, $z(t)$ is the concentration of radiotracers in blood vessels, $w(t)$ is the radiotracer concentration in the lymphatic system, $u(t)$ is the radiotracer concentration in the urinary system, β_{zx} is the rate of radiotracer capture by interstitial cells, β_{wz} is the elimination rate of radiotracers from the lymphatic system in the bloodstream, β_{xw} is the rate of radiotracer movement from the interstitium to the lymphatic system, β_{zu} is the elimination rate of radiotracers from the bloodstream. Thus, the simple system of differential equations (1) has been used to model the kinetics of radiotracers. The initial conditions are the following ones: $x(0) = 0, z(0) = 1, w(0) = 0, u(0) = 0$. Half-

decay period of ^{99m}Tc-radiotracers is equal to $T_{1/2} = 6$ hours. Functions of activity retention $x(t), z(t), w(t), u(t)$ are presented in the reduced units (normalized on unit of the injected activity).

Results

Radiotracer simulation is one of the main methods of interpretation of radionuclide research results. Quantitative data of radiotracer transport kinetics in a body are presented in the form of "activity-time" or "concentration-time", which reflects the spatial and temporal processes of change in the concentration of radioactive indicator in the "regions of interest" and characterizes the rate of ^{99m}Tc-radiotracers retention and washout in the organ/tissue. The case of intravenous administration of radiotracers was considered in the model. The aim of the paper is to describe radiotracer transport in the frame of four compartment models: the circulatory system, the lymphatic system, the interstitium, and the urinary system.

The "time-activity" curves of radiotracer transport kinetic $n(t)$ in the frame of four-compartment model describe four processes: The intake of the radiotracers by the systemic blood system and the process of radiotracer distribution in the body (Fig. 1a). The vascular curve is characterized by the rapid growth of the concentration curve in the circulatory system $z(t)$ in the first seconds after injection of radiotracers, which reflects the intake of the radiotracers by the systemic blood system and beginning the process of radiotracer accumulation. The concentration-time dependency in the interstitium $x(t)$ corresponds to the smooth amplitude growing up to the maximum value, and then entering the plateau phase, which reflects the processes of the radiotracer accumulation and retention in the interstitium (Fig.1b). The concentration-time dependency in the lymphatic system interstitium corresponds to the smooth amplitude growing up to the maximum value, and then entering the plateau phase, which reflects the processes of the radiotracer accumulation and retention in the lymphatic system ($x(t)$). The concentration-time dependency in the urinary system $u(t)$ is characterizing by rapid growth and practically linear decreasing, reflecting the process of radiotracer washout.

The case of intravenous administration of radiotracers was considered in the model. The model can be easily verified by the radioactive tracer concentration data in the circulatory/lymphatic system measured at some time points, and the obtained data can be used to determine of the transport coefficients. Time-activity dependencies were obtained and analyzed for each compartment. The proposed model can be classified as a simple model taking into account the main circulation process of radiotracers in a body. It can by improved by introduction of the additional compartments. The model can be transformed for different ways of radiotracer administration. This model allows to

estimate the transport coefficients for individual patients and forecast absorbed radiation doses in each chamber.

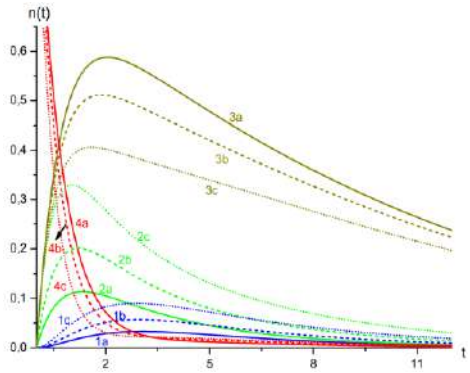

Figure 1a. Concentration versus time dependence, $\beta_{xw} = 0{,}25, \beta_{wz} = 0{,}5, \beta_{zu} = 1{,}00$.

The transport coefficient values between the circulatory system and the interstitium:

$a)\beta_{zx} = 0{,}25; b)\beta_{zx} = 0{,}5; c)\beta_{zx} = 1$.

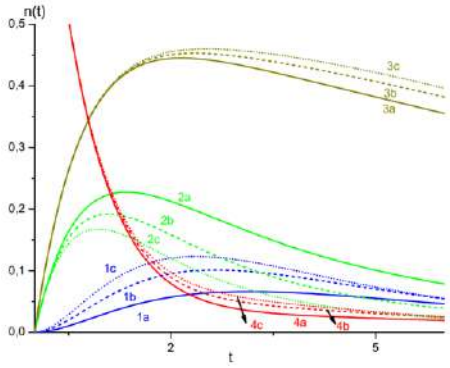

Figure 1b. Concentration versus time dependence, $\beta_{zx} = 0{,}5; \beta_{wz} = 0{,}5; \beta_{zu} = 0{,}5$. The transport coefficient values between the interstitium and the lymphatic system

$a)\beta_{xw} = 0{,}25; b)\beta_{xw} = 0{,}5; c)\beta_{xw} = 0{,}75$.

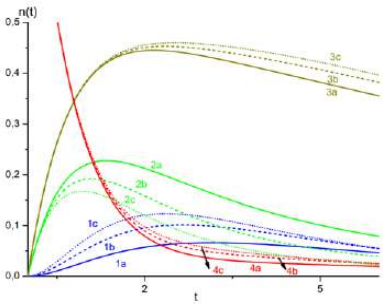

Figure 1c. Concentration-time dependence, $\beta_{zx} = 0{,}5; \beta_{wz} = 0{,}5; \beta_{zu} = 0{,}5$.

The transport coefficient between the interstitium and the lymphatic system

$a)\beta_{xw} = 0{,}25; b)\beta_{xw} = 0{,}5; c)\beta_{xw} = 0{,}75$.

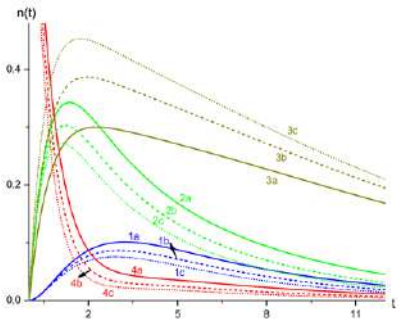

Figure 1d. Concentration-time dependence, $\beta_{zx} = 0{,}75; \beta_{xw} = 0{,}25; \beta_{wz} = 0{,}5$.

The transport coefficient values between the interstitium and the lymphatic system

$a)\beta_{zu} = 0{,}5; b)\beta_{zu} = 0{,}75; c)\beta_{zu} = 1{,}00$.

Figure 1. Concentration-time dependence. 1. The lymphatic system. 2. The interstitium. 3. The urinary system. 4. The circulatory system.

Conclusions

The proposed four-compartment mathematical model describes transport kinetics of 99m-technetium radiotracers at intravenous administration process with taking into account radiopharmaceutical accumulation, elimination and radioactive decay. Analytical solution of the model in a form of the well-known sum-of exponential solution was obtained. The dependencies of the tracer concentration

versus the time are analyzed. The model can be easily verified by the radioactive tracer concentration data in the circulatory/lymphatic system measured at some time points, and the obtained data can be used to determine of the transport coefficients. Time-activity dependencies were obtained and analyzed for each compartment. The model can be used for individual transport parameter calculation at administration by therapeutic dose loads.

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Власова О.В.

Діагностичні шкали як спосіб оцінки поліорганної недостатності при неонатальному сепсисі

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Вступ. Неонатальний сепсис є однією з причин смерті дітей. Виокремлення клінічних симптомів має низьку інформативність у діагностиці сепсису новонароджених, тому запропоновано використання їх у комплексі для оцінки тяжкості порушення стану хворих та визначення прогнозу захворювання.