Thesis annotation of
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"Pharmacokinetic aspects of directed transport of antibiotics to the focus of surgical infection with the help of cellular carriers (experimental research) ",
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Urgency

The idea of a selective distribution of medicines in the human body was obviously always relevant, but it was only possible to move towards its solution at the present time, due to the development and implementation of the methodology of directional transport in clinical practice. The tendency to create methods of targeted ("address") drug delivery and the development of transport systems designed to provide targeted delivery to the target, controlled release, obtaining a prolonged effect, increasing therapeutic effectiveness, as well as reducing its toxicity is quite clearly manifested in modern pharmacology [Kalia Y.N., Perozzo R., Scapozza L. - 2012. Allémann E., Delie F., Lange N. - 2012].

The key role in the solution of these problems is played by the transporters of medicines themselves. They allow not only to create a deposited form of the introduced compound, but also to protect the drug from premature destruction and inactivation of the reticuloendothelial system of the organism; prevent or reduce the immune and allergic reactions of the body to the injected drug; to carry out its targeted delivery to organs and target tissues [Jeong K.J., Kohane D.S. - 2011; Rodriguez-Devora J.I., Ambure S., Shi Z.D., Yuan Y., Sun W., Xui T. – 2012; Whittam A.J., Maan Z.N., Duscher D., Wong V.W., Barrera J.A., Januszyk M., Gurtner G.C. - 2016]. Autologous blood cells also can serve as micro containers carrying out the delivery of drugs to the targets. Ideas of using blood cells for the purpose of creating directional transport systems for medicines are certainly logically justified and seem to be the simplest, clinic-accessible option for solving this problem. The realization of the idea of targeted transport of drugs goes along the lines of the use of red blood cells, leukocytes, platelets as containers for drug delivery [Gutiérrez M.C., Colino Gandarillas C.I., Sayalero Marinero M.L., Lanao J.M. – 2012; Kirtane A.R., Langer R., Traverso G. - 2016]. More commonly used one is the idea of using as transporters for erythrocytes medicines. They can easily be to extracted from the blood, where they are present in large quantities, have a long enough lifetime and, as they age they are exposed in the body to the natural process of biodegradation [Millán C.G., Marinero M.L., Castañeda A.Z., Lanao J.M. Drug, - 2004; Magnani M, Pierigè F, Rossi L. - 2012]. Cellular containers for medicines, created on the basis of autologous erythrocytes, were called "pharmacocytes" [Gening T.P., Kolker I.I., Zhumadilov Zh.Sh. – 1988; Provotorov V.M., Ivanova G.A. – 2009; - Movshev B.E., Vitvitsky V.M., Lisovskaya I.L., Ataullakhanov F.I. - 2006]. A less developed transport system for antibiotics is the cellular leukocyte system, created on the basis of domestic advances [Gulyaev A.E., Zhugasheva S.K., Ermekbaeva B.A., Piven L.I., Yusifov Z.A.- 2015]. However, the prospects of such a transport system, the possibility of obtaining a significant therapeutic effect are discussed in the literature recently, especially intensively for antimicrobial and antitumor drugs [Huang W.C., Lu I.L., Chiang W.H., Lin Y.W., Tsai Y.C., Chen H.H., Chang C.W.,

Chiang C.S., Chiu H.C. – 2017; Pang L., Zhang C., Qin J., Han L., Li R., Hong C., He H., Wang J. A - 2017].

Hypothetically, cellular transport systems should change the pharmacokinetic properties for the encapsulated drug substance and provide a selective distribution of the drug with the predominant accumulation in the tissues of the reticuloendothelial system (RES) or in the clusters of cells capable of phagocytosis (abscesses, purulent foci, etc.) [Bax B.E., Bain M.D., Talbot P.J. – 1999; Briones E., Colino C.I., Millán C.G., Lanao J.M. - 2009].

It is assumed that the drug release from the cellular transport system should occur when the endocytosis / phagocytosis is destroyed on time [Rossi L., Serafini S., Pierigé F., Antonelli A., Cerasi A., Fraternale A., Chiarantini L., Magnani M. – 2005].

Thus, the probability of increasing the concentration of antibiotic in the congestion zone of phagocytirating cells is created, for example, in the zone of a purulent-inflammatory focus [Gutiérrez Millán C., Zarzuelo Castañeda A., González López F., Sayalero Marinero M.L., Lanao J.M. – 2008]. These assumptions pay special attention to antibiotics as objects for inclusion in cellular transport systems. However, the development of strategies for the use of transport systems for antibiotics based on autologous blood cells is limited by an insufficient degree of description of the characteristics of pharmacokinetics and as a consequence the inability to predict the dose regime. The lack of a proper amount of preclinical results prevents the introduction of the ideas of targeted transport to the clinic. All of the above information can be considered as arguments justifying the relevance of the development of new medicinal transport forms of antibiotics based on autologous blood cells.

The purpose of the study

Identification of the prospects of directional antibiotic transport systems on the basis of autologous blood cells according to pharmacokinetic parameters.

Objectives of the study

1. Receiving containers (transport systems) for antibiotics based on autologous blood cells, their invitro biopharmaceutical characteristics.
2. Study of the pharmacokinetics of a model antibiotic-ceftriaxone, included in autologous blood cells, with a single intravenous injection of intact rabbits.
3. Study of the pharmacokinetics of a model antibiotic-ceftriaxone, included in autologous blood cells, with a single intravenous injection of rabbits with a model of focal surgical infection.
4. Comparison of pharmacokinetic parameters of the model antibiotic included in autologous blood cells, choice of the optimal variant.

Scientific novelty

1. There was a comparison of harmacokinetics of two main targeted antibiotic transport systems based on autologous blood cells-leukocyte transport system and targeted transport system based on erythrocyte shadows, was established the advantage of the leukocyte transport system for the parameters of the half-life ($T_{1/2}$) and the area under the pharmacokinetic curve "concentration-time" (AUC).

2. The possibility of increasing the level of antibiotic concentration in the focus of bacterial purulent inflammation was proved with the administration of an antibiotic in the leukocyte transport system.
3. The results of the pharmacokinetic experiment proved the previously existing assumption that when the antibiotic is incorporated into cellular transport systems on the basis of autologous blood cells, the pharmacokinetics change in the same manner.

The main provisions for the defense

1. 1. Invitro shadows of erythrocytes and leukocyte mass of blood cells are able to reversibly bind the extracellular antibiotic ceftriaxone from the extracellular medium and gradually release most of it within a day. This type of interaction can be designated as the deposition of an antibiotic, and the resulting complex of antibiotic and autologous blood cells, as a transport cellular system.

2. Erythrocyte and leukocyte transport systems cause similar changes in the pharmacokinetics of the antibiotic included in them. The peculiarities of the pharmacokinetics of ceftriaxone with intravenous administration in the erythrocyte transport system or in the leukocyte transport system, as compared with the intravenous administration of a free antibiotic, are an increase in the half-life and apparent volume of distribution, a decrease of the elimination constant and the clearance of ceftriaxone.

3. According to pharmacokinetic parameters, the leukocyte transport system for antibiotics can be considered more promising in comparison with the erythrocyte cellular transport system.

Approbation of the work

The main provisions of the thesis are reported and discussed: in the Republican scientific and practical conference with international participation, dedicated to the 80th anniversary of Professor S.V. Lokhvitsky (Karaganda, 2015); International Scientific and Practical Conference of Young Scientists "The World of Science and Youth: New Ways of Development" (Karaganda, 2016); 5th annual international scientific and practical conference "urgent issues of medicine" (Baku, 2016); at the meeting of the Department of Surgical Diseases No. 2; on scientific-expert commission of surgical disciplines of KSMU.

The theme of the research work was approved by the Ethical Committee of the KSMU (Protocol No. 21 of November 21, 2014).

Publications

According to the materials of the thesis, 7works were published, including: 3 in scientific editions recommended by the Education and Science Control Committee of the Ministry of Education and Science of the Republic of Kazakhstan, 1 publication in the international scientific publication incoming in the information base of the Scopus company "GeorgianMedicalNews".

The structure and scope of the thesis

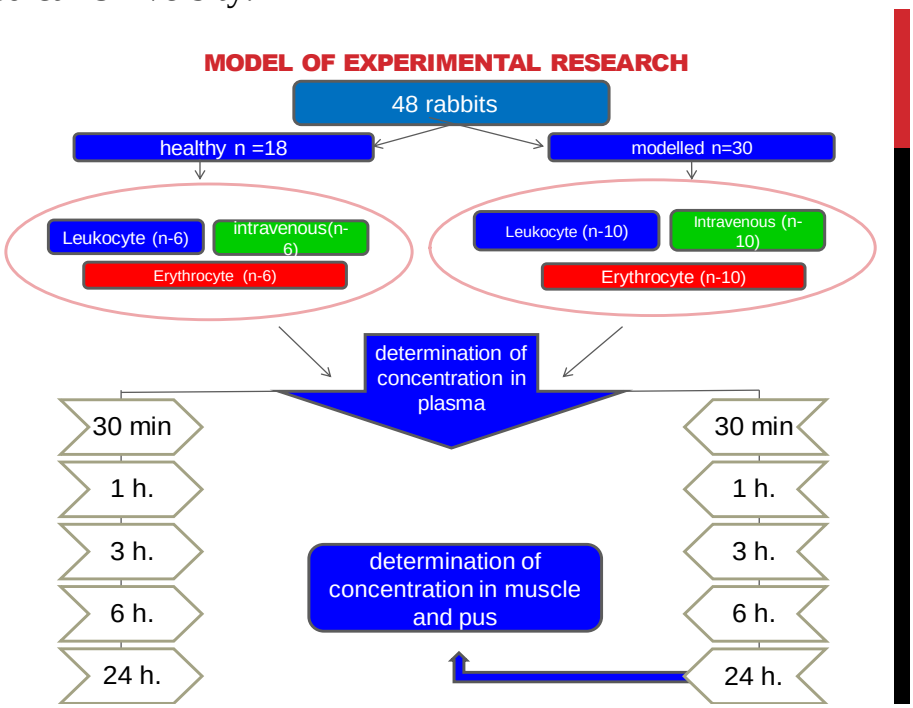
The thesis consists of an introduction, 3 sections of the main part, findings with conclusions and practical recommendations, a list of used sources, presented by 146 sources. The text is presented on 74 pages of a computer kit, illustrated with 23 tables, 22 figures.

Practical significance

The data obtained in the thesis on the possibility of directed changes in pharmacokinetics indicate the prospects for the development of antibiotic transport systems based on autologous blood cells (erythrocytes and, to a greater extent, leukocytes). Parameters of the pharmacokinetics of an antibiotic deposited in autologous blood cells established in the work may serve as a guideline for clinical trials of systems for the targeted antibiotics delivery.

Materials and methods of the research

In the experiment, there were used 48 mature male laboratory chinchilla rabbits. At the beginning of the experiment the average age was 90 ± 2.16 day. Rabbits on average weighed 2.6 ± 0.28 kg and were kept in standard conditions of the typical vivarium of the Karaganda State Medical University.



Methods of the research:

Experimental studies were conducted on the basis of SRC KSMU.

- The production of leukocyte and erythrocyte transport systems for the antibiotic ceftriaxone was carried out with the advice of NLA Nazarbayev University and the National Center of Biotechnology staff (A. Gulyaev, V. Tretak, Z. Shulgau)
- Modeling of focal surgical bacterial infection of soft tissues was carried out on chinchilla rabbits according to the generally accepted method.
- The determination of the concentration of the antibiotic ceftriaxone by HPLC method was carried out in LCU SRC KSMU, director 2013-2016. - Doctor of Medical Sciences, Professor Azizov I.S.
- Mathematical modeling of pharmacokinetics was carried out according to the program Borgia 1.03. within a one-part, two-part model with suction.

- Morphological studies were conducted with the advice of Professor M. M. Tusupbekova in the educational and scientific pathomorphological laboratory of the KSMU.
- Statistical Research Methods

Conclusions

1. When the antibiotic is incubated with ceftriaxone with the shadows of erythrocytes, up to 70% of the dose is associated and within 24 hours more than 80% of the drug dissociates to the extracellular space from the previously bound one. When invintro of the antibiotic ceftriaxone is incubated with leukocyte cell mass, it assosiates 15.6 ± 4.1% of the drug from the inserted dose, in the presence of 0.5 mM ATP binding increases to 28.5 ± 2.7% and within 24 hours the dissociation rate is more than 60% .
2. The peculiarities of the pharmacokinetics of ceftriaxone in the composition of the erythrocyte transport system in comparison with the pharmacokinetics of the free preparation when administered intravenously to intact rabbits are: decrease in the numerical value of the elimination constant (K_{el}) and an increase in the apparent volume of distribution (V) with a tendency for a decrease in total clearance (Cl), an increase in the half-life ($T_{1/2}$) and the area under the pharmacokinetic curve (AUC).
3. The peculiarities of the pharmacokinetics of ceftriaxone in the leukocyte transport system in comparison with the pharmacokinetics of the free preparation for intravenous administration to intact rabbits are: decrease in the values of the elimination constant (K_{el}), total clearance (Cl) with an increase in the apparent volume of distribution (V), an increase in the half-life (an increase $T_{1/2}$ by 1.9 times) and the area under the pharmacokinetic curve (an increase of AUC by 1.5 times).
4. The pharmacokinetics of ceftriaxone in the erythrocyte transport system in rabbits with a model of focal surgical infection is characterized by a reduced peak in serum, a slower distribution from the central chamber to the peripheral one, an increase of T1 / 2 (by 2 times), AUC and MRT (by 27- 30%), with decreased Cli and Kel and unchanged V. Tsiftriaxone when administered as part of the erythrocyte transport system accumulates in the inflammatory focus, creating a higher concentration in the inflamed th muscle. Accumulation of ceftriaxone in the focus of inflammation (pus and surrounding muscle tissue) is increased compared to the version of administration of the free drug (F increases from 0.03 to 0.09 for muscle tissue and the tendency of F increase for pus is from 0.04 to 0.05) .
5. The pharmacokinetics of ceftriaxone in the leukocyte transport system in rabbits with a model of focal surgical infection is characterized by: a reduced peak in serum, a slower distribution from the central chamber to the peripheral, an increase in T1 / 2, AUC and MRT (3-5 times) decreased Cl and Kel (by 3 times) and unchanged V. Accumulation of ceftriaxone in the focus of inflammation (pus and surrounding muscle tissue) increases (F increases from 0.03 to 0.13 for muscles and from 0.04 to 0.08 for pus) compared with the version of administration of the free preparation.
6. When the antibiotic ceftriaxone is included both in the erythrocyte transport system and in the glaucocytic transport system, the same changes in pharmacokinetic parameters are revealed: prolongation of the drug stay in the body ($T_{1/2}$, AUC and MRT increase and Cl and K_{el} decrease), as well as increased accumulation in the outbreak purulent inflammation. The difference between cellular transport systems is expressed in higher

values of $T_{1/2}$, AUC (by 1.9 and 2.2 times, respectively) and higher values of F (by 1.5 times) for the leukocyte transport system with unidirectional changes in pharmacokinetics.

7. The leukocyte transport system for antibiotics according to the parameters of pharmacokinetics can be considered more promising than the erythrocyte cell transport system, since the administration of ceftriaxone in the leukocyte transport system provides a higher level of antibiotic concentration in the focus of inflammation and retention for a longer time.

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