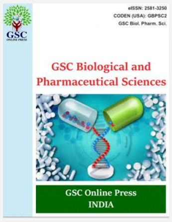
GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/



(REVIEW ARTICLE)

The use of physiotherapeutic methods for percutaneous administration of medicinal substances

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GSC Biological and Pharmaceutical Sciences, 2023, 23(02), 001–005

Publication history: Received on 21 March 2023; revised on 28 April 2023; accepted on 01 May 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.23.2.0177

Abstract

The use of transdermal drug administration under the influence of various physical fields is used to treat various types of diseases. The main characteristics that determine the conditions and speed of the physiotherapeutic procedures include: the frequency and intensity of the physical field, the exposure time period, the distance to the impact zone and the composition of the contact substance. The role of these characteristics is determined in experimental studies. In the work, a thermostat was used that maintains a temperature corresponding to the temperature of the human body.At the beginning of the experiment, the optical density of the solution containing no antibiotic was measured in the first chamber of the thermostated cell; at the same time, the growth of the antibiotic concentration in the second chamber was determined and the dependence on its growth and time was plotted. The experiments were repeated before and after switching on the source of physical fields, and the dependences of antibiotic permeability were determined with an average error of 5-6%.

Keywords: Physiotherapy; Physical fields; Antibiotics; Percutaneous administration; Muscle tissue

1. Introduction

It is known that physiotherapy studies the physiological effect of various physical factors, and also uses the methods of their application for treatment and prevention.At the same time, the physical field is used for transdermal drug administration, which is used to treat various diseases, as well as for cosmetic procedures [1,2]. Currently, the use of physical fields is increasingly replacing chemotherapy and making its use more limited. This is due to increased allergization of the population and global changes in the environmental situation in the world. Chemotherapy is also ineffective when the desired concentration of the drug in the pathological focus of treatment is reached.

In contrast, physiotherapy, as a type of complex treatment, uses in its arsenal a wide range of physical fields and a large number of drugs administered through the skin and mucous membranes using intramuscular and subcutaneous injections. The role of the physical fields involved in the treatment process is reduced not only to their direct therapeutic effect on biological tissues, expressed in thermal, force, “information”, separator and sonifying action, but also to accelerate the penetration of the drug into the area of the inflammatory process [3,4]. This variant of drug treatment allows you to effectively influence the local focus of infection without reducing the overall immunity of the body [5].In addition, it becomes possible to use non-synthetic and semi-synthetic antibiotics like the penicillin series, which are more gently tolerated by the body. The most effective is the treatment of the patient by the simultaneous action of the antibiotic and physical fields, which make it possible to accelerate its penetration into the affected tissues until the loss of its properties caused by hydrolysis and oxidation under the action of enzyme decomposition [6]. In most cases, the local impact of the physical field is reduced to the elimination of congestion due to the intensification of blood flow and cell metabolism. An increase in the transmission capacity of blood capillaries is caused by resonant mechanoelectric effects in the case of the use of magnetic and electromagnetic fields, or by acoustic resonance and micromask effects,

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*Corresponding author: Abdullaev Namik Tair for example, when using acoustic fields of various frequencies and amplitudes. Intensification, for example, of cell metabolism is carried out by changing the electrochemical potentials and properties of the lipid-protein component of cell membranes. Thus, according to the degree of change in the intensity of processes, for example, ion exchange of tissues, one can locally evaluate the effectiveness of the parameters of the physical field.

To eliminate the transfer of antibiotics in drug physiotherapy, four types of fields are mainly used: electric, magnetic, electromagnetic and acoustic. All of these fields have different phoretic properties (affecting the rate of transfer of molecules and ions) depending on their physical parameters.

2. Method for assessing the influence of physical fields

To assess the effect of physical fields on the transport of antibiotics, a technique has been developed using placental and muscle membranes in vitro that mimic the biological protective barriers of body tissues. This technique makes it possible to evaluate not only the phoretic properties of fields in relation to antibiotics, but also their overall effectiveness in stimulating metabolic processes. Conducting experiments on the study of ion exchange in vivo is a practically impossible task, in addition, the results of possible experiments have a very low reliability. Phospholipid membranes [7] or the “pence clamp” method [8] used in classical bioelectrochemistry and cytology model transfer processes only at the level of a cell wall fragment.The transfer of ions and molecules in tissues can be carried out both through the biological fluid of the surrounding cells and muscle fibers, and through the cells themselves with overcoming cell membranes. In the human body, dense lipid-protein and muscle barriers prevent the penetration of antibiotics [9].Basal parts of juvenile placental membranes are used as imitations of the lipid-protein barrier, and longitudinal sections of striated skeletal muscles were used as imitations of the muscle barrier.The large area of muscle membranes and their thickness ensure the averaging of the properties of the biological barrier. Obtaining muscle membranes with smaller thicknesses leads to their extremely low strength and to gross errors in measuring their average thickness - an important characteristic used in the calculations of mathematical models.The inhomogeneous structure of the muscle, when obtaining thinner membranes, leads to the formation of defects and distortion of the experimental results. The choice of antibiotics is associated with their minimal destructive effect on the immune system compared to modern synthetic antibiotics. The listed antibiotics are also well stable in aqueous solutions; their noticeable hydrolysis begins only after a few days, which makes it possible to prepare sufficiently large volumes of working solutions.The maxima of the spectral characteristics of levomycetin, benzylpenicillin, oxacylamine lie in the range from 195 to 310 nm, which is convenient when using spectrophotometric quantitative analysis, while there is no interfering effect of cell components that are destroyed in the process of obtaining membranes.

The use of biological tissues, as shown by the experiments, is fully justified in comparison with the use of model membranes made of synthetic materials that are not capable of fully reproducing the structure and chemical composition of biological tissues. It should be noted that some important bioelectrical properties of the studied membranes, which are characteristic of objects in vivo, are retained.

3. Experiment technique

Simulation of antibiotic transport processes through placental and muscle membranes, as well as the use of additional equipment (thermostats, emitter of physical fields) required the creation of a number of electrochemical cells of an original design. In the membrane cell, the volume of the solution is divided into two parts, and on the one hand there is a pure NaCl solution, on the other hand, the NaCl solution with an added antibiotic, which, due to a change in the concentration of the solution, moved to the opposite chamber of the cell.When studying the effect of fields, the cell was equipped with brackets, respectively, for attaching emitters of physical fields or electrodes.As a method for determining the concentrations of antibiotics in a solution, a spectrophotometric method was chosen, which makes it possible to monitor changes in the concentration of solutions in real time. Modern single-beam biochemical spectrophotometers of the «Genesys» series manufactured by «Thermo Elektron Corp.»(USA) have high sensitivity and signal stability with constant control of the optical system and halogen lamp according to the standard, as well as the possibility of direct transmission and recording of information to a computer. The ease of use of spectrophotometers and the large volumes of the cuvette chamber, which make it possible to place research cells inside the device, make it possible to create high-performance research complexes with high-quality control of measuring antibiotic concentrations [10]. During the work, the experimental cells have undergone a number of significant changes in the direction of increasing productivity and obtaining the largest number of parallel experiments that increase the reliability of the results. The choice of placental membranes as a biological barrier is not accidental. Placental membranes are widely used to study the transport of sugars and other substances dissolved in biological fluids [11, 12], firstly, because of the great interest in studying the protective properties of the placenta, and secondly, due to the ease of obtaining thin, sufficiently strong membranes with large surface area. For the experiment, the basal parts of abortion placental membranes were thoroughly cleaned to obtain a thin translucent film and prepared in formaldehyde. The membrane thicknesses were determined by the laser-interferometric method in the laboratory of laser and fiber-optic diagnostic systems. Due to the inhomogeneity of the surface, different thicknesses were obtained for different sections of the membrane. For this reason, a relative thickness of 0.1 mm was used for calculations, and a relatively large surface area of the membrane of 10–20 cm3 allows a qualitative averaging of its properties. Due to the rate of membrane degradation, 10 membranes were used. The muscle barrier model used sections of striated muscle with an area of 15 cm3 with an average thickness of 1mm-2mm.The production of muscle tissue samples with a smaller thickness leads to low strength in the so-called model membrane and its rapid destruction. The thickness and area of contact of the muscle membranes with the solution also makes it possible to average its properties over the thickness, which is an important factor for processing the results of the experiment.

4. Results and discussion

It follows from experience that the selected parameters of the membrane make it possible to obtain the maximum results of the experiment. The thickness of muscle barriers was measured with a micrometer, and the average value of ten measurements was chosen for calculations. The membranes were placed in frames representing plates, this made it possible not to damage or stretch the membranes, while maintaining their integrity. The thermostat TWL-K(50) was used in the work, which made it possible to maintain a temperature of 36.6°C, which corresponds to the temperature of the body. Frames with membranes were fixed in temperature-controlled cells. The cell has two cameras. Simultaneously, 0.15 mol of the test solution and 0.15 mol of sodium chloride solution containing 0.1% antibiotic solution were poured into two chambers. From this moment, the measurement of the optical density of the solution in the first chamber, which initially did not contain the antibiotic, began, at the same time the growth of the antibiotic concentration in the second chamber was determined, and the dependence on its growth and time was plotted.Each experiment was carried out 5 times to obtain a higher probability of the result. Figure 1 shows the kinetics of the permeability of four placental and four muscle membranes according to the anonymous cefazolin at a human body temperature of 36.60C without external influence of the physical field.

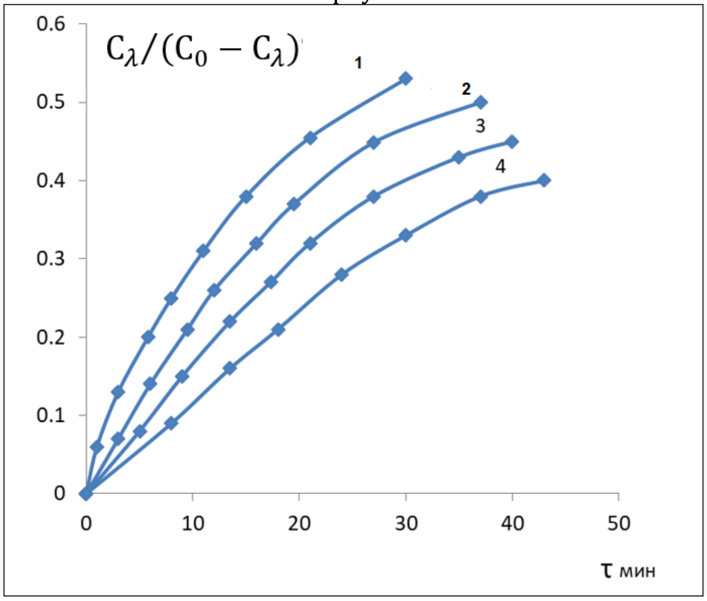

Figure 1 Kinetics of cefazolin transfer across 4 placental membranes

The figure shows that atτ<10min, the transfer of cefazolin in membrane 1 proceeds at the highest rate.At τ>10min, the experimental data on the transmembrane transfer of the cefazolin anonym are well defined in the coordinates $InC_\lambda/(C_0 - C_\lambda) - \tau^{-1}$, and the transfer proceeds along the concentration gradient at $C_\lambda/(C_0 - C_\lambda) < 1$(Fig.2).

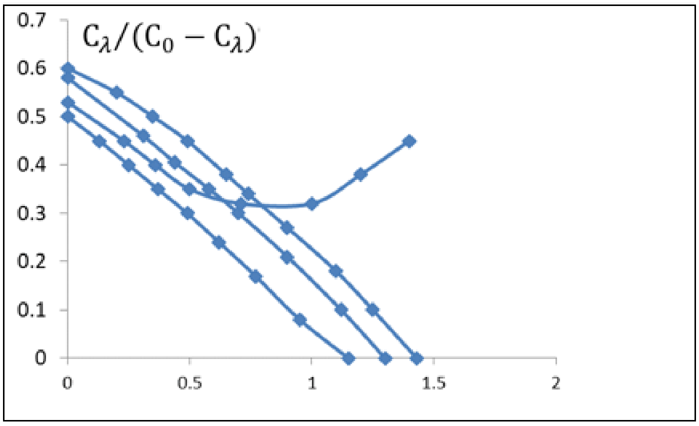

Figure 2 Logarithmic coordinates of the model

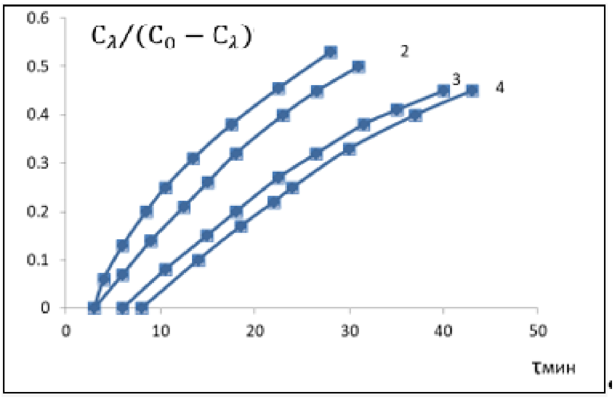

Figure 3 Kinetics of ceftriaxone transport across 4 muscle membranes in standard real-time coordinates

The kinetics of antibiotic transfer in muscle barriers is more reproducible for different membranes, this is due to the averaging of their properties over a significant thickness, as well as high values of diffusion coefficients in muscle tissues, exceeding by 2 orders of magnitude the diffusion coefficient of placental lipid-protein barriers. Due to the small thickness of the placental membranes at the time of their destruction, their sharp increase in the angle of the kinetic curve occurs. Stronger muscle membranes were replaced after changing the slope of the graph by more than 10-11%.The kinetic dependence was built on 5, less often 10 parallel measurements (Fig. 3).The kinetic dependence with a large deviation was automatically discarded.To study the influence of physical fields, we tried to use one membrane. The use of one membrane for a series of experiments is a necessary condition for obtaining quantitative results of the influence of physical fields.

5. Conclusion

After turning on the sources of physical fields, the measurement of the optical density of solutions that initially did not contain antibiotics began, at the same time, the growth of the antibiotic concentration was determined and the dependence of its growth on time was plotted. This experiment was carried out 10 times. Also conducted with an average error of 5-6% 150 experiments on the dependence of the permeability of antibiotics by anions.

Compliance with ethical standards

Acknowledgments

No conflict of interest between the three authors.

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