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BIOMECHANICAL APPROACH TO THE PROBLEMS OF BIOPHARMACY AND ENTEROSORPTION

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Abstract. The attempt to reveal aspects of interaction of biomechanics, biopharmacy and enterosorption in study of drugs and toxicants behavior in biological mediums of an organism is undertaken. The main positions and problems of biopharmacy and enterosorption are stated. The human organism data of physiological and pharmacokinetic parameters of drugs suitable for creation of mathematical models of the medicinal therapies strategy are discussed.

Key words: biopharmacy, pharmaceutical factors, biological accessibility, pharmacokinetics, enterosorption, toxicants, data bases, mathematical models

Introduction

Fundamental discoveries of the last century in the fields of biology, medicine, chemistry, physics and other sciences have led to radical transformations in pharmacy and were an incitement to the origin of biopharmacy. For the first time the main positions of biopharmacy were formulated by Wagner [1]. In Russia the first works belong to Senov, Tentsova and Azhgikhin [2, 3]. The biopharmacy is a section of science that investigates the influence of the pharmaceutical factors on therapeutic efficiency of medicinal preparations. A starting point of biopharmacy is in recognizing of biological significance of pharmaceutical processes which occur during deriving of medicinal preparations, and consideration them as complicated physico-chemical systems which are capable to enter into interaction with biological systems.

Such an approach is very close to biomechanical view of the essence of processes which develop in cells, systems and organism as a whole during passing of drug substances through diaphragms, biological mediums and systems of neutralization and excretion.

Some directions of biopharmaceutical researches are picked out, particularly

- study of the role of pharmaceutical factors;
- biological accessibility, gears and methods for its determination;
- pharmacokinetics (conditions of absorption, transport, distribution, biotransformation and exretion of drug substances);
- development of methods for identification and quantitative analysis of drug substances or their metabolites in bioliquids.

The main pharmaceutical factors are physico-chemical properties of medicinal substances (solubility, size of particles, polymorphism, availability of a charge on a surface, etc.), and also nature and amount of auxiliary substances, kind of drug form (tablets, capsules, solutions, etc.) and path of its inserting, pharmaceutical technology.

The accumulated scientific data point to inadmissibility of replacements and interchangeability of auxiliary substances during production of medicinal preparations. For example, during the study of the influence of auxiliary substances on process of absorption of medicinal substances from tablets it was ascertained that the greatest influence render the properties of connecting substances [3]. Also there is a set of examples which indicate that micronized powders of medicinal substances have in some times greater therapeutic effect than powders crushed by usual method. The medicinal and auxiliary substances are subjected to various treatments during the manufacturing of the drug form (heating, cooling, refinement, humidifying, etc.). These technological processes can change the properties of medicinal and auxiliary substances, connections between them and therefore modify therapeutic efficiency of medicinal preparations [2].

The problem of the pharmaceutical factors acquires especially large significance during research of bioequivalence of the medicinal forms. Frequently the same medicinal substance appointed in the same medicinal form, but obtained by different manufactures has different therapeutic effect. From the point of view of biopharmacy the test of bioaccessibility is used. When researching bioaccessibility by methods *in vivo* (in animals) a velocity and degree of absorption are determined. However these parameters cannot completely characterize a behavior of drug substance in organism. Hence it is required the full pharmacokinetic analysis. The experiments in animals are labour-consuming and cannot be applied under production conditions, therefore for bioaccessibility determination the methods *in vitro*, in particular the "Dissolution" test [3] are used. "Dissolution" means the quantity of active substance which under the standard conditions during certain time must shift to the solution from solid drug form, for example, from tablet. The outcomes of researches show that there is a lot of problems for which solution is necessary:

- personalizing of the "Dissolution" test, as for each medicinal substance there are conditions of maximum transition in solution;
- the comparative evaluation of correlation of *in vivo* and *in vitro* experiments which requires realization of experiments with the use of modern mathematical, pharmacokinetic and physical chemistry methods;
- development of methods to estimate the pharmacokinetic parameters which must not depend on the used gears.

The movement of medicinal substances in an organism envelopes stages of their release from the medicinal form, absorption, distribution, biotransformation (metabolism) and removing out from an organism. If the kinetics of a release of medicinal substance from the medicinal form completely depends on the pharmaceutical factors, the further medicinal substance transport depends completely on the biological factors (kind, structure, physiological conditions of mucous envelopes, cutaneous covering, muscular tissues, etc.). The medicinal operation of medicinal substance is an outcome of its interaction with cells of tissue of that or other organ. The absorption of medicinal substance begins with penetration through biological diaphragm, more often by diffusion, pinocytosis and active transport. The mathematical models of dissolution and absorption use the equation of the zero, first and second orders depending on a nature of medicinal substances and kinds of cell-like diaphragms [4]. These models express common regularities and need to be concretized in individual cases. Also it is important to study mechanisms and correlation between dissolution and absorption of medicinal substance in an organism depending on properties of medicinal substance, cell-like diaphragms and moving bioliquids.

Scientific and practical interest is in analyzing of data on safety for a share of active medicinal substance reaching receptor targets and adequate for manifestation of pharmacological effect. At the stage of release from the medicinal form this share forms not less than 75 % (interior limit under the "Dissolution" test). At the stages of absorption and

redistribution up to the blood flow system or tissue bioliquids there reaches from 10 to 90 % of liberated from the drug form of the active ingredient, the large part of which is in bind with blood proteins. The stage of biotransformation in the liver with the participation of the tissue ferments reduces a share of the active form of a drug by 90–95 %, i.e. from an initial doze entered into an organism, 1–5 % remains. Non-enteral ways for introduction of drugs (rectal, sublingual, transdermal, injection) even passing a liver, ensure in the issue approximately the same level of delivery (5–10 %) with smaller doses.

More objective information can be given by the similar analysis with allowance for nature of the acting substance concerning ability to biotransformation in groups

- non-metabolized (selected in a constant kind);
- partially or completely metabolized;
- giving active or toxic metabolites;
- pro-drugs (the only metabolites are active).

The tool and intermediate purpose for the prognosis of a biopharmaceutical behavior of medicinal substances could become a data base taking into account degree of drugs biotransformation in the above mentioned groups, chemical structure with space conformation variants, degree of biological accessibility with pharmacokinetic parameters (velocity, completeness of absorption, period of half removing out etc.), desirable therapeutic concentrations in organism's tissues and necessary doses for their reaching by various inserting ways. The final goal of creation of such data base should be the methodology of development and assignment of the rational drug forms and new medicinal preparations. To create such data base and to supply it with program possibilities for the prognosis of therapeutic efficiency for the various medicinal forms for majority of therapeutic preparation groups the collaboration of the chemists, pharmacists, clinicians, biomechanical engineers and program mathematicians is necessary.

On the other hand, there is one more area of joint interest of the above mentioned specialists. It is enterosorption, as a method for detoxication of an organism from exo- and endogenous pathological agents which have received wide application per the last years in therapeutic and valeologic doctors practice. Enterosorbents, in contrast to usual drugs, not only do not introduce into biomediums of an organism any active origin (as a rule, always xenobiotic, i.e. alien substance) but on the contrary, actively swallow up and reliably tie from intestinal contents the components being a reason or a result of various pathologies. It can be the heavy metals, exo- and endotoxines, biologically active amines, peptides and proteins, bacterial cells, their toxins and pathogenic ferments, redundant cholesterin, etc. Enterosorbents interrupt a vicious circle of repeated absorption in the digestive tract of pathological components and promote refinement of an organism, restoring its protective systems and forces [5].

The objective reason of improvement of an organism owing to clearing of slags and toxicants is the natural exchange of biological liquids with the digestive tract. So, for one day this exchange for a person makes up 6–10 liters, including more than 1 liter of a saliva, 2 liters of gastric juice, up to 0.5 liters of bile, not less than 1.5 liters of pancreatic and intestinal juices. These data in aggregate with additional performances of all interacting bioliquids (pH of a medium, availability of ferments, ionic force, osmotic activity) [6] could form the basis for creation of mathematical models from biomechanical items on following problems

- kinetics of absorption, distribution, biotransformation and elimination of various toxicants;
- mechanisms of toxicants adsorption in sorbents in biological mediums as complicated processes in multicomponent system of nonconstant composition if there is competitive sorption;

- creation of a model for an evaluation of the medicinal enterosorbent forms *in vitro* with allowance for affinity between toxicants and sorbents, their volumetric and concentration ratio, time of contact and influence of components of a biological medium with a perspective for development the "Pharmaceutical accessibility" test.
- computational model of the strategy of enterosorbents purpose taking into account initial toxicants concentration in tissues, dynamics of its elimination, doze and duration of sorbents purpose and its affinity to poison.

As a whole the final aim of all similar studies could become creation of automated consulting models for the pharmacy internists and toxicologists in development of the rational medicinal therapy.

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БИОМЕХАНИЧЕСКИЙ ПОДХОД К ПРОБЛЕМАМ БИОФАРМАЦИИ И ЭНТЕРОСОРБЦИИ

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В проблемно-методологической статье предпринята попытка выявить аспекты взаимодействия биомеханики, биофармации и энтеросорбции в изучении поведения лекарств и токсикантов в биологических средах организма. Изложены основные положения и проблемы биофармации и энтеросорбции. Обобщены физиологические параметры организма человека и фармакокинетические показатели лекарств, пригодные для создания математических моделей стратегии лекарственной терапии. Прогноз биофармацевтического поведения лекарственных веществ могла бы обеспечить база данных, учитывающая степень биотрансформации лекарственных средств, их химическую структуру с вариантами пространственной конформации, степень биологической доступности с фармакокинетическими показателями, оптимальные терапевтические концентрации в тканях организма.

Данные физиологических параметров организма в совокупности с характеристиками взаимодействующих биожидкостей могли бы послужить основой создания математических моделей по следующим проблемам: токсикокинетика, механизмы адсорбции токсикантов в биологических средах, оценка лекарственных форм энтеросорбентов *in vitro* с перспективой разработки теста "Фармацевтическая доступность", стратегия назначения энтеросорбентов.

Конечной целью подобных исследований должны стать автоматизированные экспертные системы для разработки рациональной лекарственной терапии. Библ. 6.

Ключевые слова: биофармация, фармацевтические факторы, биологическая доступность, фармакокинетика, энтеросорбция, токсиканты, базы данных, математические модели

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