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MODERN APPROACHES TO THE APPLICATION OF CARBON SORBENTS IN MEDICINE
(Literature review)

Kasimov N.A., Sadikov R.A., Khakimov D.M., Khodzhimatov G.M., Kasimov A.L., Nosirov M.M.

[1] - Republican Specialized Scientific and Practical Medical Center for Surgery named after Academician V.Vakhidov
[2] -Andijan State Medical Institute

✓ ***Resume***

At the present stage of the development of hepatology, studies aimed at improving extracorporeal detoxification technologies, in particular, the development of new high-quality hemosorbents on the basis of special types of raw materials and technologies, allowing to improve the quality of removal of toxic metabolites and reduce the risk of developing or progressing multiple organ failure. In world practice, physico-chemical characteristics, histological and morphological results of the use of various hemosorbents are continued in experimental conditions, which are able to expand the possibility of using sorption methods for blood purification during liver failure of various genes. The scientific search of methods of detoxification impact on the homeostasis system is equally important through the use of new domestic sorption materials, which will prevent the occurrence of hazardous complications that can potentially require repeated hospitalization and conducting radical treatment methods. In this direction, in particular, in improving the quality of the treatment of hepatic insufficiency, positive results were achieved by extracorporeal detox methods. At the same time, scientifically based results in the development of domestic hemosorbents and improving methods of plasmaware are required to improve the specialized medical care provided.

Keywords: medicine, carbon sorbents, classification, extracorporeal detoxification, plasmasorption.

СОВРЕМЕННЫЕ ПОДХОДЫ К ПРИМЕНЕНИЮ УГЛЕРОДНЫХ СОРБЕНТОВ В МЕДИЦИНЕ
(Обзор литературы)

Касимов Н. А., Садыков Р.А., Хакимов Д.М., Ходжиматов Г.М., Касимов А. Л., Носиров М.М.

[1] - Республиканский специализированный научно-практический медицинский центр хирургии имени академика В.Вахидова
[2] -Андижанский Государственный Медицинский Институт

✓ ***Резюме***

На современном этапе развития гепатологии перспективными остаются исследования, направленные на совершенствование технологий экстракорпоральной детоксикации, в частности, разработку новых гемосорбентов высокого качества на основе специальных видов сырья и технологий, позволяющих улучшить качество удаления токсических метаболитов и снизить риск развития или прогрессирования полиорганной недостаточности. В мировой практике продолжают исследоваться в экспериментальных условиях физико-химические характеристики, гистологические и морфологические результаты использования различных гемосорбентов, которые способны расширить возможности применения сорбционных методов очистки крови при печеночной недостаточности различного генеза. Не менее важен научный поиск способов детоксикационного воздействия на систему гомеостаза путем применения новых отечественных сорбционных материалов, что позволит предупредить возникновение опасных осложнений, которые потенциально могут потребовать повторных госпитализаций и проведения радикальных методов лечения. В этом направлении, в частности, в улучшении качества лечения печеночной недостаточности экстракорпоральными методами детоксикации достигнуты положительные результаты. Вместе с тем для улучшения оказываемой специализированной медицинской помощи требуются научно-обоснованные результаты по разработке отечественных гемосорбентов и

совершенствованию способов плазмосорбции.

Ключевые слова: медицина, углеродные сорбенты, классифицирование, экстракорпоральная детоксикация, плазмосорбция.

УГЛЕРОД СОРБЕНТЛАРНИ ТИББИЁТДА ЗАМОНАВИЙ ҚЎЛЛАНИШГА ЁНДАШУВ

Касимов Н. А., Садыков Р.А., Хакимов Д.М., Ходжиматов Г.М., Касимов А. Л., Носиров М.М.

[1]Академик В.Вохидов номидаги Республика ихтисолашган жарроҳлик илмийғамалий тиббиёт маркази
[2]Андижон давлат тиббиёт институти

✓ ***Резюме***

Гепатология ривожланишининг ҳозирги босқичида экстракорпорал детоксикация технологияларини такомиллаштиришга қаратилган тадқиқотлар, хусусан, токсик моддаларни олиб ташлаш сифатини яхшилашга имкон берадиган махсус хом ашё ва технологиялар асосида янги юқори сифатли гемосорбентларни ишлаб чиқариш метаболитлар ва полиорганик етишмовчилик ривожланиш ёки кучайиш хавфини камайтиради. Жаҳон амалиётида турли хил гемосорбентлардан фойдаланишнинг физик-кимёвий хусусиятлари, гистологик ва морфологик натижалари экспериментал шароитда давом эттирилади, улар турли генларнинг жигар етишмовчилиги пайтида қонни тозалаш учун сорбция усулларидан фойдаланиш имкониятларини кенгайтириши мумкин. Гомеостаз тизимига зарарсизлантириш таъсирининг усулларини илмий излаш янги маҳаллий сорбцион материаллардан фойдаланиш билан бир хил даражада муҳимдир, бу эса такрорий касалхонага ётқизишни ва радикал даволаш усулларини талаб қиладиган хавфли асоратлар пайдо бўлишининг олдини олади. Ушбу йўналишда, хусусан, жигар етишмовчилигини даволаш сифатини оширишда экстракорпорал детоксикация усулида ижобий натижаларга эришилди. Шу билан бирга, кўрсатиладиган ихтисослаштирилган тиббий ёрдамни такомиллаштириш учун маҳаллий гемосорбентларни ишлаб чиқариш ва плазма дастурларини такомиллаштириш бўйича илмий асосланган натижалар талаб қилинади.

Калит сўзлар: тиббиёт, углерод сорбентлари, таснифлар, экстракорпорал детоксикация, плазмосорбция.

Relevance

Environmental disasters associated with environmental pollution with industrial pesticides and household waste and, as a consequence, the increase in various diseases, which are accompanied by the accumulation of toxic substances in the human body, required a radical change in approaches to the problem of maintaining homeostasis, due to the low efficiency of pharmacotherapy [2,36].

In this regard, one of the solutions to this problem was the use in medical practice of methods of sorption detoxification of the body, which include hemosorption, removal of toxins from plasma, lymph (plasma sorption, lymphosorption); enterosorption (detoxification of the body through the gastrointestinal tract), application of sorbents (vulnerosorption) [3,5,18,28,29]. Each of these methods of sorption detoxification is based on the ability of active sorbents to remove harmful substances of various nature from the body in case of certain diseases (oncological, autoimmune, infectious, allergic, etc.) [19,35].

One of the methods directly dependent on the quality characteristics and technological aspects of medical sorbents is hemosorption (HS). Possessing the ability to adsorb various toxic substances, HS has been widely used in patients with acute renal failure since the 60s of the XX century [13, 14]. However, significant obstacles to the use of hemosorption are the trauma of blood corpuscles, especially platelets (a decrease in the level of platelets can be from 15 to 50% of the initial level), during perfusion through the sorbent, which creates a risk of severe complications and can lead to "thrombosis" sorbent [6].

At the same time, the HS has not lost its position to this day, since in order to improve the biocompatibility of carbon sorbents, various modification options have been proposed:

heparinization of granules, coating with albumin, dextran [13,34]. Research is currently underway to improve the effectiveness of this detoxification method [10,11,26,27].

The use of sorbents is primarily aimed at neutralizing the negative effects of endo- and exotoxins on the human body [1,7,9,12,20,26]. Various violations of "biochemical homeostasis" cannot but affect the systems of detoxification, excretion, and immunity of the body. The so-called "toxic pressure" leads to a cascade of subsequent disorders that the body is unable to cope with on its own or with the help of pharmacotherapy, which often contributes to a fatal outcome or to the development of a state of chronic intoxication, which aggravates the course of pathological processes. As you know, one of the promising directions in the prevention and treatment of diseases of the gastrointestinal tract (GIT) of various etiologies is the use of enterosorbents and sorption methods of detoxification. Enterosorbents used today, which are complex compounds of organic and inorganic substances, have the ability to bind toxins of various origins and prevent their absorption from the gastrointestinal tract [15].

One of the urgent tasks of organoprotection in case of body poisoning is the development of bionanotechnology based on nanodispersed carbon (a product of thermal decomposition of hydrocarbon raw materials of oil and coal origin and natural gas). At the same time, the starting material in the genesis of oil and gas is the organic sediments of large water bodies (plankton, algae, microorganisms, small animals), which, dying, form a layer of bottom silt. As it becomes denser, biochemical processes accelerate, contributing to the formation of gaseous and liquid hydrocarbons. The creation of a wide assortment of sorbents is greatly facilitated by a variety of initial carbon-containing materials and processing methods that allow them to be transformed into porous carbon materials [15].

It should be especially noted that medical sorbents that come in contact with biological fluids of the body have special quality requirements, namely, a high degree of chemical purification, a minimum content of impurities, non-toxicity, greater mechanical strength and smooth surface relief of granules, no dust formation (release of ultrafine particles), high sorption capacity in relation to the substances to be removed, compatibility with blood and inertness in relation to blood corpuscles [12,17, 23,24].

Sorbents used in medicine and their classification.

Sorbents, unloading the organs of natural detoxification, extract various exo- and endotoxins from biological media:

- products of natural metabolism in high concentrations,
- activated enzymes that can damage tissues,
- inflammatory mediators, biologically active substances,
- medium-molecular peptides of various weights,
- peroxide products,
- ingredients of non-viable tissues heterogeneous in composition,
- aggressive components of complement,
-bacterial toxins (exo- and endotoxins).

So, specifically with liver pathologies, sorbents are removed from the body - bilirubin, ammonia, bile acids, bacterial toxins, medium molecules and others; for kidney diseases - products of protein and purine metabolism (urea, uric acid, creatinine), medium molecules, electrolytes, biogenic amines, catecholamines, etc. for broncho-pulmonary diseases - kinins, catacholamines, biogenic amines, regulatory peptides, hormones, prostaglandins and other biological active substances; in diseases of the gastrointestinal tract - bacterial toxins, indole, skatole, bile acids, regulatory peptides, hormones, end and intermediate products of the main types of metabolism, gases, etc. [8,21,33].

When the sorbent comes into contact with a biological fluid, the removed substance (sorbate) interacts with the absorber-sorbent. Most of the sorbents used are not specific with respect to specific toxins and metabolites [22]. Their porous structure contains all substances that have tropism to the surface of the sorbent and the corresponding sizes of molecules that allow penetration into pores of different sizes [31].

These substances differ in relative molecular weight - from hundreds to a million daltons, hydrophilic and hydrophobic properties, features of circulation in the blood, transport through membranes, and ways of excretion from the body. For their effective removal, it is necessary to select the appropriate sorbents in terms of the size and volume of pores, the size and chemical composition of the surface, and other indicators. The list of diseases for which sorption technologies are shown is extensive - acute poisoning, allergic diseases, liver and biliary tract diseases, kidney diseases, lung diseases, acute inflammatory and purulent-septic diseases, neuropsychiatric and mental diseases, withdrawal syndromes in drug addicts and alcoholics, immunodependent diseases, consequences of injuries, acute disorders of the main types of metabolism, oncological diseases, radiation injuries. Skin diseases, endocrine diseases and others.

With regular and prolonged intake of sorbents, intestinal absorption decreases, which leads to a decrease in the energy value of food components and, as a result, to a decrease in body weight. The noted ability of dietary fiber to cause a longer feeling of satiety, to replace high-energy products, is also the basis for the use of sorbents in the treatment of obesity. At the same time, the indicators of cholesterol metabolism are restored, the abolition of the sorbent leads to an increase in the content of cholesterol, triglycerides, and the cholesterol index of atherogenicity in the blood.

These observations suggest that such a structure is one of the forms of interaction of the sorbent with biological tissue, forming a new, biomineral environment that promotes the effectiveness of sorption therapy [16].

Sorbents based on polymers

This type of sorbent (mainly for oral administration) includes materials based on plant raw materials [4]. For example, a finely dispersed powder of a bloody color Microcell is a preparation of microcrystalline cellulose obtained from cotton and wood cellulose (permission from the Ministry of Health of the Russian Federation, Reg. N 97/128 / 5 was obtained for its clinical use).

Enterosorbents based on plant raw materials include "Polyphepan", obtained in the form of secondary raw materials after hydrolysis of deciduous and coniferous wood species [15]. It consists mainly of its own lignin (80%) and hydrolyzed cellulose, is produced on an industrial scale, phenylpropane derivatives are the structural element of polyphepan. Polyphepan has a specific surface area of up to 20 m2 / g, on its surface there is a set of functional groups: metaxyl, carboxyl, carbonyl, hydroxyl and others. In terms of sorption of low and medium molecular toxins, Polyphepan is not inferior to coal. However, there are no data on the content of razilny metals in the sorbent. It can be assumed that Polyphepan also belongs to the number of sorbents that are difficult to standardize and, first of all, according to the raw material from which it is obtained. The development of the production of polymeric materials made it possible to create on their basis interesting sorption materials for medical purposes with a controlled composition, pore size and a set of functional groups. Known Enterosgel, which is a hydrogel of methylsilicic acid (CH3SiO 1.5 n H2O). After removing all moisture at a temperature of 1200C˚, the preparation turns into a xerogel with a surface of 150-250 m2 /g, with a pore volume of 2.7-3 cm3 / g, and a pore size of 100 nm. The sorbent is effective against medium-molecular toxins, does not bind electrolytes.

Silicon organic sorbents are characterized by hydrophobicity and sufficient sorption capacity in relation to organic substances.

Food additives based on pectins, cellulose, pine needles, and algae are often positioned as sorbents [32].

Sorbents based on carbon materials.

Today, the main raw materials for industrial methods of obtaining porous carbon materials are wood waste (36% of porous carbon materials are produced from bark and lignin), non-coking coal materials (28% from coal and 14% from brown coals), as well as some polymeric materials, nut shells (coconut, etc.), fruit seeds (olives, peach), carbon black, pitches, cokes (petrochemical and coke products), etc. [7,12,17,25,30].

As you know, one of the main types of raw materials for obtaining carbon sorbents are pyrolysis products of hydrocarbon raw materials of oil, coal origin and natural gas [7,12,17]. Of greatest interest are petroleum and coke-chemical raw materials obtained in the process of catalytic cracking, pyrolysis of gasoline and gas oil fractions, the process of distillation and processing of coal tar [7, 12]. In addition, synthetic materials (porous styrene-divinylbenzene copolymer, furfural, etc.) are one of the valuable carbon-containing raw materials [7,12,15,17].

To date, the production of spherical carbon sorbent granules is carried out by liquid formation of furfural granules and their carbonization and steam-gas activation, followed by washing the material with distilled water. The sorbent production technology can also include the stages of coal demineralization using acid and alkali solutions and innovative dedusting technologies by treatment with surfactant solutions [7,12,17].

Hemosorbents are conventionally divided, depending on the predominant type of bonds in the system, the extractable substance - sorbent, into two main classes: 1) neutral sorbents (activated carbons, silica gels, alumogels, neutral copolymers that do not have ionic groups); 2) ion-exchange sorbents (organic and inorganic ion exchangers of synthetic and mineral origin).

For sorption medicine, carbon, carbon-mineral, specific and immunosorbents are widely used.

Of particular interest for the sorption of toxic substances of various molecular weights and nature are carbon sorbents that meet the requirements of medicine.

It should be noted that the main properties of traditional industrial brands of active carbons used in sorption medicine are determined both by the nature of the feedstock and by the technology of their production. [7,12,15,17].

So, the most effective component of any coal sorbent is the porosity of their surface, which determines the directions of their application in sorption medicine. For example, it is advisable to use microporous carbon sorbents to remove products with a low molecular weight from biological fluids, for example, creatinine, aliphatic hydroxy acids, amino acids, uric acid, etc. [15].

The developed mesoporous structure of sorbents satisfies most of the problems of hemosorption. When removing toxic substances with a carbon sorbent with a hydrophobic surface, the main sorption mechanism is physical adsorption due to the action of dispersion forces. In this case, the efficiency of adsorption is determined by the proportionality of the molecules of the adsorbed substances and the pores (mesopores) of the sorbent.

Until recently, the regulation of the adsorption activity of the sorbent was carried out mainly by changing the porosity of the surface, i.e., the geometric modification of their structure. But. this leads to a decrease in the strength of the sorbent granules. Another way to regulate the adsorption properties of sorbents is to change the chemistry of the surface of the sorbents, to create chemically bonded functional groups on the surface of the sorbent that are capable of sorption of pathological substances of various nature.

Currently, the issue of increasing the efficiency of sorption of pathological substances is relevant in order to develop selective sorbents for their subsequent use in sorption medicine and proteomics - the science of developing methods for isolating and separating proteins from biological media and their identification.

Of particular interest are studies [15] on the use of polyarginine and betulin, which, according to the author, are priority modifiers of the carbon surface that ensure the ecological safety of sorbents (license of the Federal Service for Veterinary and Phytosanitary Surveillance of the Russian Federation for the production of veterinary medicinal products No. 00-15- 1-002530 dated 02.09.2015).

According to the author, the bifunctionality of new sorbents with betulin ("Betulin in a carbon microsphere" contains at least 98.5% carbon, at least 1% betulin and not more than 0.5% glycerin) and polyarginine ("Carbon enterosorbent with polyarginine" does not contain less than 97.5% carbon, not less than 2.5% of total nitrogen), is due to the adsorption properties of the nanoporous carbon matrix and the immunocorrective properties of the biologically active component. According to the author, the modification of the surface of the carbon enterosorbent with betulin and polyarginine leads to an increase in their adsorption properties in relation to markers of toxic substances (methylene blue and vitamin B12).

The author proved that “when using the carbon enterosorbent“ Betulin in a carbon microsphere ”at a dose of 200 mg / kg within 3 days after the antiparasitic treatment of rats with the drug Aversect-2, an increase in the indices of spontaneous and activated NBT tests was established by 11% and 15% accordingly, the prevalence of average-sized CICs in rats compared to the group of intoxicated animals. "

As for the enterosorbent modified with polyarginine, the latter “has a significantly higher adsorption capacity in relation to proteins that simulate toxic compounds of a protein nature (the degree of extraction of lysozyme is 70 ± 4%, α-lactalbumin is 63 ± 2%), compared to the original carbon sorbent (the degree of extraction of lysozyme 59 ± 2%, α-lactalbumin 57 ± 1%) ".

Studies have shown that a carbon sorbent modified with polyarginine “reduces the content of pro-inflammatory cytokines (interleukin 6, interleukin 8, tumor necrosis factor) in the blood plasma of rats with acute 253 experimental peritonitis. Their levels after sorption decrease: for interleukin 6 to 22.20 ± 0.50 pg / ml, interleukin 8 - to 0.95 ± 0.06 pg / ml, tumor necrosis factor - to 1.20 ± 0.03 pg / ml. Before the introduction of sorbents, the levels of cytokines were, respectively: 26.40 ± 1.20, 3.10 ± 0.20 and 2.25 ± 0.75 pg / ml ".

Significant interest in the development and improvement of carbon sorbents has become the reason for a large number of dissertation research carried out in the Russian Federation over the past 10 years [7, 12, 15, 17].

For example, [12] proposed oxidative activation of carbon materials “to be considered as a topochemical reaction, including the stages of adsorption (chemisorption) of an oxidizing agent on the active sites of the substrate (the surface of the initial carbon material) and subsequent interaction with the substrate, leading to the formation of pores”. The author found that "the porous space of the formed carbon sorbent is significantly affected by the graphitization and crystallite size of the starting material." Changing the size of the crystallites can improve the characteristics of the pores of the sorbent. In another dissertation research [7], a technology was developed for obtaining a mesoporous carbon sorbent for medical use based on Sibunit ™ material, which, according to the author, “surpasses known medical carbon sorbents in terms of hemocompatibility and adsorption activity with respect to compounds with an average molecular weight. Based on the results of clinical trials, it was recommended to use it in the treatment of diseases occurring with the formation and accumulation of precisely toxins of a given molecular weight. "

Conclusion

Thus, the causal relationship of a violation of the synthetic, metabolic and detoxifying functions of the liver in its acute or chronic damage is the accumulation of various toxic substances, such as inflammatory cytokines, oxidative stress mediators, ammonia degradation products, bile acids, nitric oxide, lactate, products metabolism of arachidonic acid, endogenous benzodiazepines, indoles, mercaptans, which lead to systemic damage to the body - microcirculation disorders, coagulation and immunological disorders.

Over the past several decades, researchers have been looking for methods of temporary effective replacement of the functions of the damaged organ. Today, most clinical studies on organ replacement and organ protection pursue several goals: removal of toxins to create conditions for the regeneration of their own hepatocytes; resolving the issue of transplantation; creation of conditions for the restoration of the function of the donor liver after transplantation.

Currently, the methods of extracorporeal prosthetics of liver function in the complex of treatment of liver failure are divided mainly into two approaches: with the use of biological substances and without them. If biological systems include hepatocytes or whole organs (of human origin or derived from animals), then the approach without biological substrates is based on dialysis, filtration or adsorption techniques. The most common adsorptive methods of detoxification are hemo- and enterosorption, purification of plasma and lymph (plasmasorption, lymphosorption), application of sorbents (vulnerosorption). The unresolved problems of extracorporeal detoxification include the compatibility of adsorbents with blood and the specificity of the elimination effect. Most unmodified sorbents are "aggressive" with respect to blood corpuscles and "blind" with respect to adsorbing substances. Several ways of solving these problems have been identified.

So, one of them is the creation of coatings for sorbent granules or the widespread use of perfusion, in which the contact of blood corpuscles with adsorbents is completely or partially excluded. The accepted postulate when using sorbents and technologies with their use is the provision that sorbents should not have their own pharmacological action, and changes detected against the background of their use are associated with the phenomena of adsorption of metabolites, microorganisms, biologically active substances, etc., formed in internal environments.

The development and research of new, effective, non-toxic sorbents for the prevention and treatment of gastrointestinal diseases, regulation of metabolism, increasing resistance is an urgent task of medicine. Currently, in medical practice, carbon sorbents with high efficiency and safety of use are of the greatest interest. At the same time, the creation of carbon materials with increased adsorption activity in relation to toxic substances of a certain nature, with detoxifying and corrective properties by regulating the chemical nature of their surface (chemical modification) is of considerable interest, thereby expanding the spectrum of biospecific sorbents.

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