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Enterosorption method in the treatment of intoxication syndrome

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Summary

The work focuses on the role of the toxic syndrome and endointoxemia in the pathogenesis of infectious and noninfectious diseases. Enterosorption method in the treatment of endotoxemia is analyzed.

Keywords

Endotoxemia, enterosorption, sorbents.

Intoxication (Latin In - in, into, Greek toxikon - poison) – life disoroder caused by toxic substances entering the body from the outside (exogenous intoxication) or formed inside (endogenous intoxication). Exogenous intoxication is often identified with the concept of "poisoning", while endogenous is called "autointoxication", "endotoxemia", and it is caused by metabolic products formed in the body in the dynamics of development of various pathological conditions, and largely determines severity and outcome of sorption processes in the disease. Study simulation experiment makes it possible to determine chronobiological sequence of endotoxemia formation: from the source of toxemia (colon) endogenous pathological substances enter blood, where they bind to plasma protein molecules (albumin and lipoproteins), and then into fixation and biotransformation organs (liver, immune system, lungs), excretion organs (liver, kidneys, GIT, lungs, skin) as well as deposition organs and tissues (adipose tissue, nervous system, bones, endocrine system organs, lymphoid tissue) [1]. This syndrome is accompanied by a large number of diseases, therefore, it is multifactorial in origin and develops the accumulation of endotoxins of various nature and composition. These include natural metabolites products in high concentrations, activated enzymes, inflammatory mediators, medium-sized substances of different nature, peroxide products and other biologically active substances, heterogeneous components of devitalized tissues, aggressive complement components as well as bacterial exo- and endotoxins.

Endogenous intoxication syndrome in infectious disease often occurs with the intestinal infection caused by accumulation of endotoxins - lipopolysaccharides associated with the outer membrane of bacteria and consisting of lipid A, core polysaccharide, and the side chain - O-polysaccharide. The most significant bacterial endotoxins are gram-negative ones. On the outside wall of a gram-negative bacterium up to 3.5 million lipopolysaccharide molecules may be placed. After apoptosis of the bacterial cells, endotoxin molecules remain biologically active. In addition to LPS, the outer wall of gram-negative bacteria includes proteins, since the outer membrane consists of 3/4 lipopolysaccharides, while 1/4 accounts for of the protein components. Together with LPS these proteins form lipopolysaccharide-protein complexes of different size and molecular weight. These complexes are called bacterial endotoxins, and it is these complexes that provide structural integrity of the bacteria determining antigenic and pathogenic properties of bacteria [2].

Endotoxins formed in the gastrointestinal tract cause degradation of proteins and lipids of host cells, inhibit oxidative processes and synthesis. Endotoxins have a direct and indirect impact on the structure of cells, systems and organs (remote effect). [3]

At the level of cellular structures endotoxins have cytolytic effect; they activate lysosomal enzymes; block energy processes in the mitochondria; initiate synthesis of free radicals; inhibit synthetic processes in the ribosomes. Remote effect of endotoxins is an expressed microcirculation lesion in the form of isolated extra- and intravascular disorders and combined changes. Extravascular changes relate to the regulation of peripheral vascular tone, while the large part of intravascular changes is rheological blood disorders and disorders of transcapillary and transmembrane exchange.

The term "endotoxin" indicates that the toxin is a part of the cell and not a substance secreted to the environment. Endotoxin is a potent stimulator of the synthesis of cytokines, particularly of tumor necrosis factor (TNF) and other pro-inflammatory interleukins, which, in turn, activate neutrophils, endothelial cells, and platelets. Furthermore, endotoxins cause release of other mediators: platelet activating factor, complement components, kinins, histamine, and endorphins. That is, so-called "mediator chaos" is formed against the background of endotoxemia, with the development of cell hypoxia and metabolic disorders. The resulting biologically active substances affect the cardiovascular system, reducing total peripheral vascular resistance and vascular tone. Under the influence of bacterial endotoxins internal clotting mechanisms are activated leading to the development of coagulation disorders in the microvasculature, impaired blood flow, and tissue ischemia. As a result of blood clotting, thrombosis and embolism of small vessels occur. Lipid A, a part of the lipopolysaccharide, causes fever, disseminated intravascular coagulation syndrome and shock. Cytokines participating in this process, - IL-1 and TNF produced by macrophages, increase vascular permeability, change endothelium properties and influence thermoregulatory center of the hypothalamus, causing hyperthermia.

Endotoxin aggression is qualified as a universal mechanism involved in the pathogenesis of many diseases of infectious and non-infectious origin [4]. The role of pathology of various organs and systems of the gastrointestinal tract (fermentopathy, helicobacter infection, violation of gut microbiota) has been proved in the disorders of the digestive barrier of GIT mucosa, accompanied by a decrease in the activity of nonspecific protection factors, reducing production of secretory IgA, and increasing accumulation of histamine, kinins and pro-inflammatory cytokines. The resulting pathological process causes the increased permeability of the mucous membrane for toxins, allergens, their increased absorption of endotoxin with formation of a chronic syndrome, which is one of the major triggers of allergic sensitization and implementation of inflammation in the skin [5, 6]. According to Shamov et al. [4], plasma concentration of endotoxin in acute atopic dermatitis in children is ten times greater than the reference rate. Therapy of acute pathological GIT disorders reduces activity of endotoxemia, thus significantly reducing activity and severity of the allergic process. [7]

Role of endotoxemia in the recurrent and latent pyelonephritis and renal failure in children has been demonstrated by studies of Bagdasarova et al. [8]. Determination of endotoxemia markers - leukocyte intoxication index, activity of autologous serum – has allowed the authors to conclude about its importance in exacerbation of pyelonephritis. It has been confirmed the effectiveness of enterosorption method of elimination therapy in treatment of the disease.

Development of enditixemia (metabolic intoxication) due to metabolic disorders in patients with acute and chronic liver disease of various origins has been described by academician Gromashevskiy [9]. Accumulation of toxic products on this background, especially of medium-weight molecules, largely determines the outcome. Enterosorption in liver failure is comparable to other detoxification methods. Its use has determined significant reduction of toxic and metabolic liver load, thereby mitigating the severity of liver failure [10]. On the background of enterosorption normalization of the digestive function of the intestine and intestinal microbiota was noted as well.

As the GIT secretory and excretory function, infectious and inflammatory diseases of various organs are accompanied by accumulation of the decay products, toxins, and various factors accompanying any inflammatory process, in the intestine. That is, in severe pathological process, especially of infectious and inflammatory character, the intestinal tract "stores" toxic metabolic products. For example, in case of burns [11], along with invasion of microorganisms detected in the burn wound, microbial disorders in the intestine are noted, with digestive processes disorder, bacterial contamination, development of maldigestion and malabsorption syndromes, increased formation of bacterial amino acid metabolites (indole, skatole) and, as a consequence, aggravation of endotoxemia. In this case, increased permeability of the intestinal wall to endotoxins produced for a long time causes chronic toxicosis, creating conditions for sensitization and autosensitization.

Combination with intestinal endotoxemia is characteristic for septic diseases - meningoencephalitis, peritonitis, abscesses, etc. in connection with the existing discharge of bacterial toxins from the blood in the GIT [12-14].

Intestinal infections of both viral and bacterial etiology are always accompanied endotoxicosis [15-17].

Exogenous compounds penetrating the GIT from the outside also cause severe toxemia. They include toxic substances of various origins, as well as xenobiotics - heavy metals, pesticides, household chemicals, dyes, preservatives, drugs, etc. [18].

Thus, endotoxin aggression is qualified as a universal mechanism involved in pathogenesis of many diseases of infectious and noninfectious origin, emerging with the massive arrival of endotoxin on the background of insufficient activity of secretory systems. At the same time current therapy aimed at neutralizing endotoxin effects (antibodies to lipid A, and TNF-α, IL-receptor blocker 1) is ineffective. Under these conditions, an important role in the complex treatment of patients belongs to sorption methods [19].

Among the methods of toxicosis mitigation, binding and elimination of toxins enterosorption is the most simple, inexpensive and physiologic method with possible use for a long time and even during the lifetime, such as chronic hepatic or renal insufficiency. Enterosorption is a treatment of intoxication syndrome in different diseases, based on the ability of enterosorbents to bind and excrete a variety of exogenous substances, microorganisms and their toxins, endogenous intermediate and final metabolites that can accumulate or penetrate into the GIT cavity in the pathological process. Enterosorption is included in the efferent therapy group (from the Latin *efferens* - output), i.e. a group of therapeutic measures, aim at termination of the toxins of various origins and their elimination from the body. Along with enterosorption, this group includes hemodialysis, peritoneal dialysis, plasmapheresis, hemosorption etc.

Enterosorbents have a high sorption capacity without being destroyed in the GIT, and are capable of binding exogenous and endogenous agents (microorganisms and their toxins, poisons, excessive metabolites and other harmful substances) by adsorption and absorption, ion exchange or complexation. Enterosorbents absorb endo- and exotoxins from multicomponent solutions, moreover, substances with macro- and mesopores can fix bacteria and viruses on their surface, i.e. have etiotropic effect. At the same time, enterosorbents bind toxic products normally formed in the intestines without changing the composition of the normal intestinal microflora. But the most significant pathogenic feature of enterosorption is its detoxification effect associated with the absorption of toxic products, not only produced, but also secreted in the intestine. Chymus modification by sorbents is of certain importance.

Therapeutic effect of enterosorbents is based on physic and chemical properties of the sorbent capable of binding and excreting toxic products (sorbates). The sorption capacity (capacity of the sorbent) is determined by the ability to absorb the substance, fix and display it. Sorption capacity of a sorbent depends on the presence of the porous structure, which has an active surface. Depending on the radius of the pores, three types exist: micropores, with radius less than 1.5 nm, mesopores having a radius of 1.5 to 200 nm and macropores - more than 200 nm. The listed species hasvedifferent mechanisms of the processes. Small molecules are adsorbed mainly in the micropores, while meso- and macropores serve a transport channels for them. Micropores are for molecules of moderate and high molecular weight practically inaccessible, while they are adsorbed in the mesopores. Macropores serve for sorption of supramolecular structures and cells.

Sorption processes are carried out by four main ways. The first of them is adsorption, which is the interaction between the sorbent and the sorbate at the interface. Adsorbents have a porous base, which promotes accumulation in the pores, and fixation of the agents due to their physicochemical properties. This reduces the concentration of adsorbed substances in the environment, i.e. in the GIT lumen. The second way is absorption, when sorbent absorbs the entire volume of sorbate, i.e. it holds the solutes. The third way is ion exchange, when there is a replacement of ions on the surface of the sorbent with sorbate ions (ion exchange resins). The fourth way of sorption is complexation, a complex combination of neutralization process, transport and excretion of antigens, metabolic products (bilirubin) etc.

The history of use of enterosorbents dates back for thousands of years: in Egypt over three thousand years ago, charcoal was applied for outdoor and indoor use. Thousands of years ago healers of China, India and Greece used charcoal, clay, pounded tuffs or burnt horn to treat poisoning, intestinal disorders, jaundice and other diseases. In ancient Russia birch charcoal or bone was used for this purpose. According to historical versions, appointment of charcoal after poisoning saved the life of Alexander Nevsky. Charcoal powder was used to sprinkle the wound, pounded charcoal was given *per os* to children and adults with diarrhea. Avicenna first proposed enterosorption methods as prevention: in his "Canon of Medicine", referring to the art of preserving health, he named clearing the body from the excess among one of seven basic methods. In the XVIII century, physicists described sorption properties of coal, and in Russia the successor of M.V. Lomonosov, I.E. Lovitz (1757-1804) in 1785, studying the chemical properties of charcoal, justify the use of enterosorption.

In the late 1970s a new generation of sorbents appeared, with high and selective sorption capacity for metabolites and toxic substances. The accident at the Chernobyl nuclear power plant, when there was an urgent need for protection of the affected people from the received radionuclides, was a boost. There is a growing interest in enterosorbent connected with the deteriorating state of the environment, especially in the large cities, where environmental hazards exceed the allowed bounds, and foods do not meet the standards. The need for enterosorption and hemosorbents repeatedly increases in natural disasters, accidents at industrial facilities. Currently, the value of enterosorption in nutrition and dietetics increases. *Per os* administration is the most effective for enterosorbents, as sorption process begins in the stomach, and concludes in the small intestine.

Table 1. direct and indirect therapeutic effects of enterosorption

Direct action	Indirect action
Sorption of toxins and xenobiotics incoming *per os*	Prevention or reduction of toxic-allergical reactions
Sorption of endogenous secretion and hydrolysis products	Correction of metabolism and immune status. Correction of disbalance of biologically active substances
Binding of gases	Regeneration of integral and permeable mucosa
Irritation of GIT combining sites	Improvement of intestinal blood supply
Stimulation of intestinal motility	Potentiating correcting and detoxification effects.

Enterosorption method is closely associated with the issues of nutrition and dietetics, interest in which has increased dramatically in the recent years and has become of social importance in some countries.

National and international programs for prevention and treatment of atherosclerosis have been formed and started to be implemented, where sorption of cholesterol and bile acids takes one of the main places.

Binding of gases in the putrid fermentation gases makes it possible to eliminate bloating and improve intestinal blood supply during enterosorption. Passing through the gastrointestinal tract, sorbents can enhance intestinal motility and evacuation of intestinal contents due to irritation of the receptor site.

The list of direct and indirect mechanisms of therapeutic effects of enterosorbents is much longer than in the above article. This method of efferent therapy affects the function of all organs and systems, as evidenced by a variety of clinical effects in the treatment of patients with different pathological processes.

Table 2. Positive changes of biochemical and hematological values in enterosorption

Change	**Pathological process**
Reduction of endotoxemia symptoms (decreased leukocytosis, LII, decreased toxic neutrophils and plasma toxicity)	Acute inflammation, oncology diseases
Normalization of free-radical processes (malondialdehyde, diene conjugates, hydroperoxides), biologically active substances	Ischemic processes, inflammation
Reduction of metabolites (oligopeptides, urea, creatinine, bilirubin, residual nitrogen), glucose	Oncology diseases, exo- and endotoxemia
Inhibition of blood activity (ALT, AST, amylase, trypsin, lipase)	Acute inflammation
Improved values of lipid metabolism (cholesterol, triglycerides, β-lipoproteins)	Hypertensive disease, sclerosis
Improved cell and humoral immunity, decreased sensitization (increased T-lymphocytes, decreasing eosinophilia, blast-transformation reaction, CIC and normalization of IgM and IgE)	Allergy diseases

Enterosorbents currently used are classified as follows:

- Carbon adsorbents based on activated charcoal (carbolen, carboctin, gastrosorb), granular coal (SCN, SKT-6A SUGS, SCAN, etc.) and coal-fiber materials (vaulen, actilen, "Dnepr");

- ion exchange materials or resins (layxalate, cholestyramine);

- lignin-based enterosrbents (polyphepanum, lignosorb);

- polyvinylpyrrolidone derivatives (enterodez, enterosorb);

- polymethylsiloxane polymer (Enterosgel);

- sorbents used for GIT diseases, the effects of which are due to their viscosity and not their binding capacity (white clay, aluminum hydroxide, Almagelum, Gastal, sucralfate, silica gels, zeolites);

- natural dietary fiber: cereal bran, cellulose, alginates (Detoxal), pectins (Polysorbovit-50, Polysorbovit-95), chitosan. The most commonly used carbon sorbents and enterosorbents are based on polyvinylpyrrolidone.

When choosing a drug, the doctor must take into account the following requirements for available enterosorbents: high adsorption efficiency with full safety and non-toxicity; good biocompatibility with the tissues; high sorption capacity towards the substances removed; selective sorption of medium-weight toxic metabolites; no damaging effect on the mucous membrane of the stomach and intestines; no impact or a positive impact on the process of secretion and intestinal microbiocenosis; convenient pharmaceutical form.

Spectrum of the used enterosorbents is now extensive. Comparative characteristics of modern enterosorbents used in clinical practice is shown in Table. 3. Among them are widely used in practice, including pediatric, ***Enterosgel*** reserved.

Table 3. Comparative characteristics of modern enterosorbents used in the clinical praxis

Name	Influence on the mucous membranes	Adsorption capacity	Dose	Duration of treatment
Enterosgel – hydrogel of methylsilicic acid, the only highly selective enterosorbent	Cytoprotective action, without destroying membrane digestion	4.5-5.0, sorption selectivity 70-1,000 U, pathogenic flora adhesion	Under 1 year – 5 g/day 2-7 years – 10 g/day 7-10 years – 10-20 g/day Grownups – up to 30 g/day	6 months
Smecta – a drug from special clay sorts	Protects GIT mucosa	3.6, adsorbs viruses and pathogenic microflora	1-3 sachets a day	10-15 days
Algisorb – algae polymer	Does not destroy GIT mucosa	2.6, heavy metal salts, radioactive isotopes	1 g for 1 year of life	10-15 days
Filtrum-STI – wood processing product	Does not destroy GIT mucosa	3.5	1-3 tablets 3 times a day	10-15 days
Lactofiltrum – 65% hydrolyzed lignin + 6% lactulose	Does not destroy GIT mucosa	3.5	0.5-2 tablets 3-4 times a day	10-15 days
Activated charcoal (carbolen)	Destroys GIT mucosa after 5-7 days	1.8-2.0	1 g for 1 year of life	7-10 days
Polyphepanum – product of wood grain (lignin)	Destroys GIT mucosa after 5-7 days	2.0-2.2	0.5-1.0 g for 1 kg of body mass	3-7 days
Microsorb-P – granulated coal sorbent	Destroys GIT mucosa after 10-14 days	2.2-2.4	1 g for 1 year of life	3-5 days

Along with elimination of toxic substances and correction of gut microbiota, Enterosgel contributes to restoration of the epithelium of the GIT mucous membranes [20]. Sorption detoxification properties of Enterosgel are due to the porous globular structure (sponge-like), mostly with an average pore diameter. This allows to bind and remove toxic substances with a molecular weight of 70-1000 Da - protein metabolites, bilirubin, cholesterol, urea, creatinine [21]. The sorbent has a high biocompatibility.

The bactericidal properties of Enterosgel are due to the fact that it binds and removes pathogens from the blood, their metabolites and decomposition products, and does not bind the minerals, vitamins and essential, important substances for human life [22, 23]. Enterosgel binds and removes gram-positive and gram-negative bacteria, *Candida* fungi, viruses [24, 25]. It neither adhere nor suppress saprophytic intestinal microflora (lactobacilli, bifidobacteria, etc.) [26, 27].

The data indicate that Enterosgel is a highly selective enterosorbent, it has a wide range and the highest sorption selectivity factor, its long-term use is possible - up to six months. Enterosgel has the following properties:

- Safe in use, harmless;

- Large adsorption capacity, 2.5 times higher than in other types of sorbents;

- Cytoprotective properties;

- High biocompatibility with intestinal tissues;

- Non-traumatic, does not damage GIT mucous membranes;

- Hydrophobic, does not penetrate through GIT mucous membranes;

- Forms hydrogel enveloping mucosa;

- Adheres pathogenic organisms;

- Selectively acts on the intestinal microbiocenosis.

At various pathologies accompanied by endotoxemia high efficiency of Enterosgel detoxification has been revealed. In ***severe burns in children*** there was a significant decrease in the level of intoxication syndrome, an improvement of the disease and a decrease in complications [11]. On the background of restoration of normal intestinal microflora the authors found improved performance and reduced non-specific resistance markers of intoxication.

When using Enterosgel, relief of pathological symptoms in **atopic dermatitis in children** is much faster than with conventional therapies: hyperemia and skin infiltration is significantly reduced by day 3 - 4 of treatment with Enterosgel, itchy skin significantly decreases by day 7 of the therapy [7, 28, 29].

In ***atopic dermatitis in children***, the authors recommend to administer Enterosgel twice a day 1.5-2 hours before eating (fasting in the morning) and / or 2 hours after a meal or medication. A method for preparing Enterosgel for children is to dissolve it in the warm drinking water 1:10. The duration of treatment with Enterosgel in atopic dermatitis in children is up to 2-4 weeks [30, 31].

High clinical efficacy of Enterosgel in gastroenterological patients, its positive effect on the intestinal mucosa, digestion and absorption processes, composition of intestinal microflora, immunomodulator effect was identified in a large number of studies [9, 24, 26, 32, 33]. A significant therapeutic effect in the treatment with **Enterosgel** was reached in severe intoxication caused by intestinal infections in children [34], which determines its detoxifying properties and neutralization of the infectious agent.

The sorbent is taken orally 3 times a day, washed down with water. Enterosgel is taken between meals and medications (1.5-2 hours or 2 hours after a meal or medication). The single dose for adults - 15 g (1 tablespoon), daily – 45 g. For children under 3 years the dose is 5 grams (a teaspoon) twice a day, daily dose – 10 g. For children from 3 to 5 years a dose is 5 grams (a teaspoon), daily - 15 g; 5-14 years old: single dose - 10 grams (teaspoon), daily dose – 30 g. Enterosgel is ready for use. Duration of treatment -

7-14 days. In chronic intoxications, Enterosgel is taken at a dose 30 grams per day for 7-10 days monthly, in allergic states – for 2-3 weeks.

In severe intoxication and acute poisoning a double dose is prescribed during the first 3 days; if necessary, long-term administration (up to 60 days) is possible (for liver cirrhosis, obstructive jaundice, etc.).

Thus, dysmetabolic processes developing in severe different diseases determine the increased formation of toxic metabolites, biologically active substances, inflammatory factors, etc., having toxic effects on the human body. In most cases, the place of their accumulation is the gastrointestinal tract. Toxic products enter the digestive organs from the inside and outside - toxic substances, xenobiotics, infection. Therefore, neutralization of endo- and exotoxins, infectious agents (viruses and pathogenic bacteria) in the GIT and their elimination by enterosorption is the most important part in relieving the toxic manifestations of infectious, allergic, septic nature, cancer, gastrointestinal and other diseases that can reduce their severity and accelerate recovery.

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