

## **SCIENTIFIC REPORT**

"Study of the character of influence of the drug Enterosgel ® on severity of intoxication in healthy individuals"

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## **Abstract**

Parameters of the report: the report consists of 36 pages, contains 9 tables, 4 figures, 1 appendix and 15 references.

**List of keywords:** *enterosorbtion, alcohol, enterosgel.*

In this research possibility of using the drug Enterosgel<sup>®</sup>, appointed to reduce severity of intoxication in healthy individuals, has been scientifically substantiated.

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## **List of Abbreviations**

VAS - visual analogue scale

GIT – Gastrointestinal Tract

## **Introduction**

Approximately 5-10% of the adult population are the persons suffering from alcoholism or consuming alcohol regularly or in large quantities. In everyday life a small amount of alcohol reduces sense of tension, fear, loneliness, frustration, boredom, depression. Hopelessness, helplessness, panic, loss of self-control that accompany many adverse life circumstances can be mitigated or even eliminated with a small amount of alcohol intake. It is the influence of alcohol on the psyche that leads to its wide consumption by the population, as intake of alcohol enhances mood, aids interpersonal communication, gives a pleasant feeling-, increases the pleasure of communicating. At the same time alcohol is predominantly not consumed alone, so it is called "social lubricant" [11].

In the modern classification of mental disorders, according to the International Classification of Diseases (ICD-10), status of acute alcohol intoxication (F10.0) is defined, to which the simple drunkenness also belongs [9, 11].

Simple alcohol intoxication refers to the consequences of drinking characterized by appearance of reversible pathological mental, neurological and somatovegetative reactions associated with

general toxic effects on the body, which is typically expressed by euphoria, sociability, relaxation and sedation.

There are three degrees of intoxication:

Mild intoxication causes festive mood, self-confidence, sense of comfort, increased activity, and cheerfulness. These symptoms are accompanied by pleasant physical sensations such as warmth and relaxation. Subsequently, fatigue grows,

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| ~~Thinking-thinking~~ becomes retarded, expressed judgments sound imprecise. At the same time, alongside with euphoric component, conflict and aggression may arise. At this level of intoxication, blood alcohol concentration is in the range of 50-150 mg/dL.

| With an average degree of intoxication emotional and behavioral disorders ~~appear~~ are more pronounced as well as increased motor excitement, euphoria easily changes to irritability and can be even replaced by depression. Proneness to conflict becomes intensive, while impulses are disinhibited. Blood alcohol concentration at this level of intoxication is 150-250 mg/dL.

In case of severe intoxication profound disturbance of consciousness up to and including sopor or coma, lack of coordination of movements are developed, speech becomes completely slurred, association are jerky-. When a patient ~~exits-recover~~ from this state, amnesia is detected. Blood alcohol concentration in severe intoxication is 300-500 mg/dL. When the concentration of alcohol in the blood reaches a level of 600 mmol /l or more, death can occur.

| Development of alcohol intoxication is caused by absorption of alcohol into the bloodstream from the gastrointestinal tract (GIT), ~~which has its own characteristics~~. [11] ~~Intake-Absorption~~ of alcohol starts in the oral cavity and extends to the stomach, and with the evacuation of stomach

contents ~~suction-absorption~~ continues in the proximal small intestine, mainly in the duodenum. In the distal small intestine a small portion of alcohol is absorbed. On an average about 20% of alcohol volume is absorbed in the stomach and the remaining 80% - in the small intestine. After absorption in the gastrointestinal tract, 80-90% of ethanol in the blood is metabolized in the cytoplasm of hepatocytes, and the rest undergoes biotransformation in the lungs, kidney, vascular endothelium and other tissues. Ethanol oxidation in the body occurs with

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alcoholdehydrogenase , whereby acetaldehyde is formed which is a highly toxic product that is subsequently oxidized to acetate . Acetaldehyde has a negative impact on a variety of biochemical processes: it violates most of the metabolic processes as well as negatively changes structure and functional activity of tissues. It is action of acetaldehyde that is a reason of a toxic effect of alcohol on the body.

Despite ~~the struggle of the society against drunkenness and alcohol abuse~~ declining in the past 5 years on 30 %, level of alcohol consumption is traditionally high in ~~our country~~ Russia.

Moreover, of course, as a consequence of a significant amount of drunk alcohol abstinence syndrome is often developed among the population: not only men, but also women in Russia suffer from a hangover syndrome. Poor health, intoxication with alcohol metabolic products, dyspeptic disorders and inability to control the situation evokes feeling of illness, while in people who drink little - shame and remorse. In people who drink often, negative emotions disappear with disappearance of a hangover syndrome that occurs most rapidly after consuming additional portions of alcohol , but the situation could repeated, and it is not always possible to deal with. In

such cases, self-treatment including traditional medicine and symptomatic drugs, for example against nausea and headache, is not always fast and efficient. It should also be noted that in case of the persons who do not abuse of alcohol, there may be situations in which the need to drink is not always determined by a person's direct desire and is caused by a set of present circumstances, for whatever reason it is so. Many examples can be given when a person who drinks little is forced to take a dose of alcohol at work in connection with the arrival of the superiors, for the better contact with a client or

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the chief etc. ~~It~~ is also probable that a person has drunk a small amount of alcohol after a busy week, but urgently needs to contact public authorities or institutions concerning an urgent problem, to drive a vehicle after a certain time, etc.

To predict the rate of absorption of alcohol and speed of intoxication development and, therefore, of sobriety, various factors are considered, among which the most important is the nature of the food received ~~together~~ with the alcohol. It is well known that products such as potatoes, meat, fatty meals slow down absorption of alcohol. Absorption of alcohol is also dependent on the existing gastrointestinal pathologies - for example, in case of peptic ulcer and gastritis rate of alcohol absorption is higher than in healthy individuals. It has also been found out that in people who abuse alcohol, alcohol absorption rate is higher than that of the others.

In reference with the above, of a large interest is the search of the drugs that could speed up elimination of the products of alcohol metabolism, reduce the degree of intoxication and severity of abstinence symptoms and accelerate the onset of a sober state with minimal adverse events associated with the action of the drug.

According to international standards, in case of acute poisoning by exogenous toxins the use of intracorporeal detoxification is recommended using absorbents, which include enterosorbents ~~group~~. Unlike invasive techniques, enterosorption is based on oral intake of health aids that can adsorb various toxic substances of endo- and exogenous origin in the gut without reacting with them, therefore it is a safe method of treatment [12]. For binding of the toxins in the body and their subsequent elimination drugs are used that can adsorb low- and middle toxic agents

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on the surface of the active substances. Releasing the body from endogenous and exogenous toxins is carried out by means of adsorption in the gastrointestinal tract and in the blood stream followed by elimination of the urine and feces. [15]

The term "enterosorption" was introduced by V.G. Nikolaev et al. in 1983 [2, 13] to indicate a new method of adsorption treatment. Based on the example of carbon enterosorbents known since the nineteenth century, first summarizes of the main mechanisms of action of this therapy were made by the authors: absorption of toxic substances entering the gastrointestinal tract, oral absorption of the toxins diffusing into the lumen of the blood, binding of toxic substances emitted with digestive juices; absorption of toxic metabolites formed directly in the digestive tract; sorption diet modification, transfer and fixation of physiologically active substances (enzymes, bile acids etc. ), on the surface of the sorbents; volume change of indigestible residue and the original properties of intestinal contents, on the basis similar to the presence herein of dietary fiber. A classical property of enterosorbents is their lack of penetration in the gastrointestinal mucosa, i.e. absence of systemic pharmacokinetics [14].

Besides activated carbon, silicon adsorbents, ion exchange resins, fiber etc are currently believed to be enterosorbents [10].

Classification of sorbents:

1. Carbon enterosorbents of I-IV generations.
2. Enterosorbents based on natural and synthetic resins, polymers and synthetic non-digestible lipids.
3. Silicon-containing enterosorbents, including silicones, aerosils and clay.

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Natural organic enterosorbents on the basis of dietary fibers, hydrolytic lignin, chitin, pectins and alginates.

5. Combined enterosorbents, part of which may include two or more types of these enterosorbents.

Presence in enterosorbents of such properties as absorption of the intestine exotoxins, xenobiotics, bacteria, bacterial toxins and other toxic products produced in the intestine (phenol, skatole, aromatic amino acids etc.) as well as potential allergens, allowing their use in the treatment of acute and chronic poisoning, acute and chronic infectious diseases of the digestive tract [14].

Presence of highly sorptive materials in the lumen of the gastrointestinal tract can substantially modify enterohepatic circulation of bile acids, amino acids, hormones, lipids, drugs and some poisons as well as use multiple administration of the absorbents to enhance natural clearance of the toxins [1, 2, 5, 7]. In this regard, it is believed that stimulation of secretion of digestive juices promotes manifestation of enterosorption medicinal properties. Enterosorbents having an indirect effect can also significantly increase excretion in the intestinal lumen of endotoxins from the internal environment of the organism (for example, products of alcohol metabolism) and thus indirectly enhance metabolism of detoxification organs as well as process of removing these substances [10, 12, 14]. An important mechanism of enterosorption is also an intraenteric transfer of physiologically active substances due to their immobilization on the sorbent surface protecting them from degradation of these agents and absorption while maintaining their functional properties in immobilized form or as further competitive desorption [10, 12].

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Among this class of drugs silicon enterosorbents should be highlighted. The most common drug among synthetic siliceous enterosorbents is Enterosgel<sup>®</sup>, which is hydroxide methylsilicic acid gel synthesized by means of water or alcohol whose organophilic properties are associated with the presence of interfacial methyl groups, and hydrophilic properties - with the presence of - OH groups, while porosity ( 150-300 m<sup>2</sup>/g) is formed by the spaces between microglobules in the material having dimensions of about 50 nm and filled with water [ 8, 15]. Enterosgel is characterized by small capacity for the substances of low and medium molar weight, but at the same time adsorption of such dyes as bromphenol blue ( 670 Da) and Congo red (698 Da) with their close molecular weights can vary up to 2.5 times, demonstrating existence of known selectivity of absorption for Enterosgel.

Enterosgel<sup>®</sup>, as well as charcoal, is also capable of accelerated transfer of physiologically active substances between different parts of GIT. Due to large differences in the spectrum and intensity of sorption activity, Enterosgel<sup>®</sup> and carbon adsorbents can be considered in a certain sense as complementary medical devices.

Given that Enterosgel® is a highly efficient enterosorbent, we have researched the nature of its impact on the degree of alcohol intoxication in healthy individuals.

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### **Study purposes**

The purpose of this study was to examine the nature of the influence of the drug Enterosgel® on severity of alcohol intoxication in healthy individuals.

### **Research objectives**

1. To assess an amount of ethanol vapor in the air exhaled by healthy volunteers 6 hours after ingestion of standard doses of alcohol and a standardized meal.
2. To assess an amount of ethanol vapor in the air exhaled by healthy volunteers 6 hours after ingestion of standard doses of alcohol, a standardized meal and 2 doses of Enterosgel MD®.

3. To assess the dynamics of detected changes in concentration of alcohol in the vapor of exhaled air in healthy volunteers receiving no Enterosgel<sup>®</sup> and in patients receiving Enterosgel<sup>®</sup>.

## **Materials and methods**

Object of study: 5 healthy male volunteers aged 28 to 33 years.

The present study was open (during the treatment doctors, researchers and healthy volunteers participating in the study knew whether a volunteer received the preparation as well as time of administration), comparative (comparison of different modes of administration of the medical device to the control supervision).

Inclusion criteria were as follows:

1. Age from 25 to 40 years.
2. Male gender.
3. Body mass index 20-25 kg/m<sup>2</sup>.

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Ability to understand information about the study and to sign an informed consent.

Exclusion criteria were as follows:

1. Alcohol abuse or habitual drunkenness in history.
2. Poor tolerance of alcoholic beverages.
3. Female.
4. Presence of any internal diseases at the time of participation in the study.
5. Presence of any internal diseases in history.

## **Description of the study drug**

Commercial product name: Enterosgel®.

Producer: "TNK Silma". **Zaitseva str. 8 , 8399851, Dankov, Lipetsk region .**

Phone / Fax: (495) 223-91-00, [www.enterosgel.ru](http://www.enterosgel.ru) , e-mail:

[contact@enterosgel.ru](mailto:contact@enterosgel.ru) .

Nonproprietary or grouping name: polymethylsiloxane polyhydrate.

Chemical name: 1,1,3,3 polycondensation product of a nonlinear - tetrahydroxy -1, 3 - dimetildisiloxane polyhydrate. .

Dosage Form: Paste for oral administration.

Composition per 100 g product. Active ingredient: polymethylsiloxane polyhydrate (nonlinear polycondensation product of 1,1,3,3 -tetrahydroxy -1, 3- dimetildisiloxane polyhydrate ) – 70 g. Excipients: purified water – 30 g.

Description: homogeneous paste of white to off- white color, odorless.

Pharmacotherapeutic group: enterosorbents . ATC Code. A 07 B

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Pharmacological properties: Enterosgel® is a porous silicon matrix (molecular sponge) of hydrophobic nature characterized by sorption properties with respect to only middle toxic metabolites (molar mass from 70 to 1000). Enterosgel® has pronounced sorption and detoxifying properties. In the lumen of the gastrointestinal tract it binds and removes endogenous and exogenous toxic substances of different nature, including bacteria and bacterial toxins, antigens, food allergens, drugs and poisons, heavy metals, alcohol. The drug also absorbs some of the metabolism products of the body, including excess bilirubin, urea, cholesterol and lipid complexes as well as metabolites responsible for the development of endogenous toxemia. Enterosgel® does not reduce absorption of vitamins and minerals, helps to restore impaired intestinal microflora and does not affect its motor function.

Pharmacokinetics: The drug is not absorbed in the gastrointestinal tract and is excreted unchanged within 12 hours.

Indications: Adults and children as a means of detoxification

- acute and chronic toxicity of different origin;
- acute poisoning with potent and poisonous substances , including drugs and alcohol, alkaloids, salts of heavy metals;
- acute intestinal infection of any origin in the complex therapy (toxic infection, salmonellosis, dysentery, diarrhea syndrome of infectious origin, goiter);
- purulent- septic diseases accompanied by severe intoxication , in the complex therapy;
- food and drug allergy;

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hyperbilirubinemia ( hepatitis ) and hyperazotemia ( chronic renal failure );

- to prevent chronic poisoning in workers of hazardous industries (occupational exposure to chemical agents of polytropic action, xenobiotics, incorporated radionuclides, lead compounds, mercury, arsenic, petroleum products, organic solvents, nitrogen oxides, carbon, fluoride, salts of heavy metals ) .

Contraindications: Individual intolerance of the drug, intestinal atony.

Pregnancy and lactation: Enterosgel<sup>®</sup> is not contraindicated during pregnancy and lactation.

Dosage and administration: Enterosgel® paste is taken orally 1-2 hours before or after eating or taking other medicines and is washed down with water. It is recommended to take the amount of the drug by stirring it in an amount of water three times as large as that of the drug at a room temperature or to take it orally and wash down with water.

Dosage for adults - 1 pack or 22.5 g (1.5 tablespoon) 3 times a day. The daily dose is 67.5 g (3 pack).

Side effects: nausea, constipation. Patients with severe renal or hepatic insufficiency may experience feeling of disgust to the drug.

Overdose: Cases of overdose have not been identified. Interaction with other drugs. Absorption of other drugs can decrease when taken with Enterosgel®.

Specific guidance. The drug can be used in complex therapy with other drugs in compliance with rules of a separate administration time - 1-2 hours before or after administration of other drugs.

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Form: Paste for oral administration in plastic cups 225 g, 450 g, in tubes of composite materials 225 g or in combined sachets 22.5 g

Storage conditions: to store at a temperature not below +4 ° C, out of reach of children. Protect from drying out after opening the package. Protect from freezing. Shelf life. 3 years. Do not use after the expiry date printed on the package.

Terms of supply for pharmacies. Without a prescription.

## Study design

To minimize the impact of exclusion on the results of research confounding factors (confounders), such as differences in the intensity of absorption of alcohol, especially individual metabolic differences in body weight and so on, the study was conducted on five healthy volunteers, each of whom has paid six visits, cross-over design was used in the study in which liquidation period for each of the participants was not less than 12 hours. Homogeneity of the observed group was due to the absence of gender differences (all participants - men), similar constitutional data (body mass index of participants was within 20-25 kg/m<sup>2</sup>), lack of digestive diseases and absence of alcohol abuse facts from history. To eliminate the influence of amount and composition of food eaten on alcohol absorption processes in the gastrointestinal tract food taken after alcohol consumption ( so-called "starter") was standardized: after drinking each volunteer ate a sandwich consisting of 30 g of white bread , 30 g of cheese and 30 g of sausage ( a standardized breakfast).

The visits differed in alcohol dose and administration of the study drug.

Plan of the visits is presented in Table 1.

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**Table 1**

Scheme of the visits

Visit	Dose of alcohol	Intake of Enterosgel®
A	100 ml	-
B	100 ml	60 minutes after alcohol intake

C	100 ml	120 min after intake of alcohol
D	200 ml	-
E	200 ml	60 minutes after alcohol intake
F	200 ml	120 min after intake of alcohol

Activities performed during the visits A, B, C, D, E and F:

**A.** On the day of the visit a healthy volunteer took in a certain alcoholic drink (whiskey *Jameson*, 40%) in a volume of 100 ml and immediately after drinking the alcoholic beverage took a standardized breakfast. 30 minutes after receiving an alcoholic drink determination of alcohol vapor in exhaled air with a breath alcohol detection device began, then a study was performed repeatedly every 30 minutes until the amount of exhaled ethanol reached zero. Starting from the 30th minute from the intake of alcohol and then every 30 minutes, the patient noted the degree of intoxication on the visual analogue scale.

**B.** On the day of the visit a healthy volunteer took in a certain alcoholic drink (whiskey *Jameson*, 40%) in a volume of 100 ml and immediately after drinking alcohol took a standardized breakfast. 30 minutes after receiving an alcoholic drink determination of alcohol vapor in exhaled air with a breath alcohol detection device began, then a study was performed repeatedly every 30 minutes until the amount of exhaled ethanol reached zero. 60 minutes after intake of alcoholic beverages a study participant took 2 doses of study medication *Enterosgel*<sup>®</sup> (45 g).

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Starting from the 30th minute from the intake of alcohol and then every 30 minutes, the patient noted the degree of intoxication on the visual analogue scale.

**Visit C.** On the day of the visit a healthy volunteer took in a certain alcoholic drink (whiskey *Jameson*, 40%) in a volume of 100 ml and immediately after drinking alcohol took a standardized breakfast. 30 minutes after receiving an alcoholic drink determination of alcohol vapor in exhaled air with a breath alcohol detection device began, then a study was performed repeatedly every 30 minutes until the amount of exhaled ethanol reached zero. 120 minutes after intake of alcoholic beverages a study participant took 2 doses of study medication *Enterosgel*<sup>®</sup> (45 g).

Starting from the 30th minute from the intake of alcohol and then every 30 minutes, the patient noted the degree of intoxication on the visual analogue scale.

**Visit D.** On the day of the visit a healthy volunteer took in a certain alcoholic drink (whiskey *Jameson*, 40%) in a volume of 100 ml and immediately after drinking alcohol took a standardized breakfast. 30 minutes after receiving an alcoholic drink determination of alcohol vapor in exhaled air with a breath alcohol detection device began, then a study was performed repeatedly every 30 minutes until the amount of exhaled ethanol reached zero. 30 minutes after

intake of alcoholic beverages a study participant took 2 doses of study medication Enterosgel® (45 g).

Starting from the 30th minute from the intake of alcohol and then every 30 minutes, the patient noted the degree of intoxication on the visual analogue scale.

**E.** On the day of the visit a healthy volunteer took in a certain alcoholic drink (whiskey Jameson, 40%) in a volume of 100 ml and immediately after drinking alcohol took a standardized breakfast. 30 minutes after

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drinking alcohol vapor content was determined in exhaled air using a breathalyzer. Then a study receiving an alcoholic drink determination of alcohol vapor in exhaled air with a breath alcohol detection device began, then a study was performed repeatedly every 30 minutes until the amount of exhaled ethanol reached zero. 60 minutes after intake of alcoholic beverages a study participant took 2 doses of study medication Enterosgel® (45 g).

Starting from the 30th minute from the intake of alcohol and then every 30 minutes, the patient noted the degree of intoxication on the visual analogue scale.

**Visit F.** On the day of the visit a healthy volunteer took in a certain alcoholic drink (whiskey Jameson, 40%) in a volume of 100 ml and immediately after drinking alcohol took a standardized breakfast. 30 minutes after receiving an alcoholic drink determination of alcohol vapor in exhaled air with a breath alcohol detection device began, then a study was performed repeatedly every 30 minutes until the amount of exhaled ethanol reached zero. 120 minutes after intake of alcoholic beverages a study participant took 2 doses of study medication Enterosgel® (45 g).

Starting from the 30th minute from the intake of alcohol and then every 30 minutes, the patient noted the degree of intoxication on the visual analogue scale.

Determination of the amount of ethanol vapor in exhaled air was performed using alcohol detection device "Alcotest 6810" (manufactured by «Draeger Safety AG & Co. KGaA», Germany). In accordance with the rules of operation of the device measurements were carried out with the following requirements:

- analyzed air samples must not contain particles of tobacco smoke, alcohol or medication residues containing alcohol from the oral cavity, as well as sputum and saliva: before the test

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at least 2 minutes must pass after smoking, at least 20 minutes after ingestion of alcohol-containing preparations.

- Before measuring the examinee must breathe normally, not till hyperventilation (rapid breaths).
- When measuring the examinee must provide the required flow rate and volume of exhaled air, exhaled air flow must be constant (non-stop) .

Evaluation of subjective experience the degree of intoxication was performed using a visual analogue scale: a volunteer pointed cross at the degree of intoxication at a 10 - centimeter scale, where 10 cm was the line with the highest possible degree of intoxication , 0 cm - with no sense of intoxication.

## **Statistical data processing**

Statistical analysis was performed using IBM SPSS 20.0.

Given the small number of observation group (5 persons) and, therefore, impossibility of conclusion about normality of distribution of the analyzed variation series, were applied paired nonparametric criteria. To describe the trends an average median was used because it is insensitive to the "-release" of the estimated figure. Measures of variation (quartiles) were not used because of their low information content for a small number of observation group (5 persons).

To detect statistically significant differences between the values of the variational series changes in the level of ethanol in exhaled air paired Wilcoxon test was used. Using this criterion pairwise comparison of data obtained was held

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for the results of the visits A, B and C , and pairwise comparison of data obtained was held separately for a result of visits D, E and F. For a single comparison of variational series level of statistical significance at which the null hypothesis was rejected, was taken equal to 0,05 ( $p = 0.05$ ). In this study, multiple pairwise comparisons were carried out in this connection, taking into account the Bonferroni correction, correction of critical level  $p$  was performed, which is calculated by the formula  $p' = p / m$ , where  $m$  - number of comparisons conducted.

## **Results of the study**

All healthy volunteers included in the study completed the study and completed all the scheduled visits. None of the healthy volunteers included in the study has not refused to take the study drug.

### **Visits A, B and C**

During the visits, A, B and C the dose of an alcoholic beverage used (whiskey *Jameson* 40 %) was in amount of 100 ml.

Dynamics of median amount of ethanol vapor in the exhaled air is shown in Table 2. and Figure 1.

Table 2. **Trends in the number of ethanol vapor in exhaled air**

Visit	Visit median amount of ethanol vapor in exhaled air , mg / l							
	0 min	30 min	60 min	90 min	120 min	150 min	180 min	210 min
A	0,00	0,11	0,13	0,10	0,09	0,07	0,05	0,00
B	0,00	0,14	0,13*	0,12	0,08	0,07	0,03	0,00
C	0,00	0,13	0,11	0,10	0,08*	0,06	0,03	0,00

**Trends in the number of ethanol vapor in exhaled air**

**visits to A, B and C**

**Visit median amount of ethanol vapor in exhaled air , mg / l**

**0 min 30 min 60 min 90 min 120 min 150 min 180 min 210 min**

**A 0,00 0,11 0,13 0,10 0,09 0,07 0,05 0,00**

**B 0,00 0,14 0,13 \* 0,12 0,08 0,07 0,03 0,00**

**C 0,00 0,13 0,11 0,10 0,08 \* 0,06 0,03 0,00**

\* Measure, after which the study participant took the drug in an amount Enterosgel® 45 mg

Figure 1. Dynamics of median amount of ethanol vapor in the air exhaled by visits A, B and C. Along the abscissa - Time ( min) and the ordinate - number of ethanol vapor in the exhaled air ( mg / l)

Given the complex shape of the curve , reflecting the median amount of ethanol vapor in the exhaled air and the differences of its maximum level, the starting point was taken 60 minutes from the moment of alcohol intake ( while receiving study drug at visit B): the dynamics of the amount of ethanol vapor in exhaled air was analyzed from this moment .

Figure 2 shows the dynamics of reducing the amount of ethanol vapor in the exhaled air, starting from the 60th minute from the intake of alcohol.

Figure 2 . Reduced amounts of ethanol vapor in the air exhaled by visits A, B and C. Along the abscissa - Time ( min) , vertical axis - the degree of reducing the amount of ethanol vapor in the exhaled air ( mg / l)

The results of pairwise comparisons using Wilcoxon test of time series variation amount of ethanol vapor in the exhaled air showed no statistical differences between the dynamics of the analyzed indicator during visits A, B and C. The values of the Wilcoxon test (Z) and the reached statistical significance (p) are presented in table 3.

Table 3

Value of Wilcoxon test for pairwise comparison of visits A, B and C

Statistic comparing visits

<u>Statistic</u>	<u>comparing visits</u>		
	<u>B - A</u>	<u>C - A</u>	<u>C - B</u>
<b><u>Value Wilcoxon test (Z)</u></b>	<u>-0,272</u>	<u>-1,633</u>	<u>-1,633</u>
<b><u>Level of statistical significance (p)</u></b>	<u>0,785</u>	<u>0,102</u>	<u>0,102</u>

**B - A C - A C - B**

**Value Wilcoxon test (Z) -0,272 -1,633 -1,633**

**Level of statistical significance (p) 0,785 0,102 0,102**

Noteworthy is that in the control point corresponding to 180 minutes (3 hours after alcohol ingestion) median concentration of alcohol vapor in the breath on visits B and C was almost 2 times

lower than in the control visit A (0,05 mg / l at visit A 0.03 mg / l at visits B and C), which shows presence of the effect of the study drug, even without confirming tendency with the statistical methods.

**Visits D, E and F**

During the visits, D, E and F a dose of alcoholic drink used (whiskey «Jameson» 40 %) was 200 ml.

Dynamics of median amount of ethanol vapor in the air exhaled is presented in Table 4 and Figure 3.

Table 4

Trends in the number of ethanol vapor in the exhaled air at visits D, E and F

V i s i t	Visit median amount of ethanol vapor in exhaled air , mg / l														
	0	3	60	9	12	1	1	2	2	2	3	3	3	3	4
	m	m	m	m	m	m	m	m	m	m	m	m	m	m	m
	i	i	i	i	i	i	i	i	i	i	i	i	i	i	i
	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
D	0	0,32	0,36	0,36	0,33	0,33	0,29	0,25	0,25	0,22	0,19	0,15	0,07	0,03	0
E	0	0,41	0,41*	0,35	0,31	0,31	0,26	0,22	0,22	0,18	0,14	0,11	0,06	0,04	0
F	0	0,27	0,41	0,37	0,36*	0,31	0,27	0,25	0,25	0,17	0,14	0,11	0,08	0,04	0

**Visit median amount of ethanol vapor in exhaled air , mg / l**

**0 min 30 min 60 min 90 min 120 min 150 min 180 min 210 min 240 min  
270 min 300 min 330 min 360 min 390 min 420 min**

**D 0 0.32 0.36 0.36 0.33 0.33 0.29 0.25 0.25 0.22 0.19 0.15 0.07 0.03 0**

**E 0 0.41 0.41 \* 0.35 0.31 0.31 0.26 0.22 0.21 0.18 0.14 0.11 0.06 0.04 0**

**F 0 0.27 0.41 0.37 0.36 \* 0.31 0.27 0.25 0.19 0.17 0.14 0.11 0.08 0.04 0**

\* Measure, after which the study participant took the drug Enterosgel® in an amount 45 g.

The starting point also takes 60 minutes from the moment of reception of alcohol (during the study drug on visit E), and the dynamics of the quantity of ethanol vapor in the exhaled air was analyzed starting from this moment.

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Fig. 3. Dynamics of median amount of ethanol vapor in the air exhaled at visits D, E and F. On the abscissa - Time (min) and the ordinate - number of ethanol vapor in the exhaled air (mg / l)

Figure 4 shows the dynamics of reducing of the amount of ethanol vapor in the exhaled air, starting from the 60th minute from the intake of alcohol. This diagram shows that the curve corresponding to visit D, located above the curves corresponding to visits E and F, indicates low rate of excretion of intoxication at visit D in comparison with the other two visits. Curves of E and F visits are laminated to each other all over the figure, except for the initial portion of the 60th to 150 minutes, where they differ. This divergence is presumably due to the fact that the

study medication at visit E was taken 60 min before (and therefore had an effect started earlier ) than at visit F.

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Fig. 4. Reduced amounts of ethanol vapor in the air exhaled by visits D, E and F. On the horizontal axis - time (min), on the vertical axis - the degree of reducing the amount of ethanol vapor in the exhaled air (mg /l)

The results of pairwise comparisons using Wilcoxon test of time series variation amount of ethanol vapor in the exhaled air are presented showing statistical differences between the dynamics of the analyzed indicator during visits D and E, and the statistical differences between the dynamics of the analyzed indicator during visits D and F. In this case, statistically significant differences between the dynamics of the index for visits E and F have been identified. Wilcoxon test values (Z) and reached statistical significance (p) are presented in Table 5.

Table 5

Value Wilcoxon test for pairwise comparison of visits D, E and F

<b>Statistic</b>	<b>comparing visits</b>		
	<u>E - D</u>	<u>F - D</u>	<u>E - F</u>
<b><u>Value Wilcoxon test (Z)</u></b>	-3,068	-3,068	-1,450
<b><u>Level of statistical significance (p)</u></b>	<u>0,002*</u>	<u>0,002*</u>	<u>0,147</u>

**Statistic comparing visits**

**E - D F - D E - F**

**Value Wilcoxon test (Z) -3,068 -3,068 -1,450**

**Level of statistical significance (p) 0,002 \* 0,002 \* 0,147**

**\* P '<0,017**

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Noteworthy is that the greatest differences in the rate of decline in the concentration of alcohol in the breath between the control visit and visits D E and F were observed in the period from 150 to 330 minutes ( see Figure 4), i.e. during this time interval study drug effect was most

pronounced . In this case the calculated maximum difference was observed in the control point corresponding to 240 minutes, i.e. 4 hours after alcohol intake: D control visit at the median amount of ethanol vapor in the exhaled air decreased by only 0.11 mg / l, and at visits E and F – by 0.20 and 0.22 mg / L, respectively.

### **Subjective assessment of the degree of intoxication**

Subjective assessment of the degree of intoxication was performed using a visual analogue scale (VAS).

After receiving an alcohol drink every 30 minutes patients noted subjective feeling of drunkenness with cross streaked on a 10- centimeter scale , which corresponds to 0 cm lack of feeling of intoxication, and 10 cm - maximum feeling of intoxication.

Due to the fact that the assessment of the degree of intoxication was not carried out continuously, and at certain periods of time from the start of observation ( binary data type) for statistical comparison counts the number of 30 -minute intervals , during which volunteers marked values different from 0 cm on VAS, i.e. number of 30-minute intervals, during which the patient felt intoxicated.

Average number of 30-minute periods and the corresponding length of the period during which volunteers subjectively noted the state of intoxication, are presented in Table 6.

Table 6

Subjective duration of sobering at visits A, B and C

<u>Visit</u>	<u>The average number of 30-minute period</u>	<u>the average length of sobriety</u>
<u>A</u>	<u>5,6</u>	<u>not more than 170 minutes</u>
<u>B</u>	<u>4,6</u>	<u>not more than 150 minutes</u>
<u>C</u>	<u>4,6</u>	<u>not more than 150 minutes</u>

**Visiting The average number of 30-minute period, the average length of sobriety**

**A 5,6 not more than 170 minutes**

**B 4,6 not more than 150 minutes**

**C 4,6 not more than 150 minutes**

Wilcoxon test values (Z) and reached statistical significance (p) are presented in Table 7.

Table 7

Value Wilcoxon test for pairwise comparison of visits A, B and C

<u>Statistic</u>	<u>comparing visits</u>		
	<u>B - A</u>	<u>C - A</u>	<u>C - B</u>
<u>Value Wilcoxon test (Z)</u>	<u>-1,633</u>	<u>= 1,633</u>	<u>0</u>
<u>Level of statistical significance (p)</u>	<u>0,102</u>	<u>0,102</u>	<u>1,000</u>

**Statistic comparing visits**

**B - A C - A C - B**

**Value Wilcoxon test (Z) -1,633 -1,633 0**

**Level of statistical significance (p) 0,102 0,102 1,000**

**Visits D, E and F**

Average number of 30-minute periods and the corresponding length of the period during which volunteers subjectively noted the state of intoxication , are presented in Table 8.

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Table 8

Subjective duration sobering visits to D, E and F

<b><u>Visit</u></b>	<b><u>The average number of 30-minute period</u></b>	<b><u>the average length of sobriety</u></b>
<u>D</u>	<u>7,8</u>	<b><u>not more than 230 minutes</u></b>
<u>E</u>	<u>8,4</u>	<b><u>not more than 250 minutes</u></b>
<u>F</u>	<u>8,0</u>	<b><u>Not more than 240 minutes</u></b>

**Visiting The average number of 30-minute period, the average length of sobriety**

**D 7,8 not more than 230 minutes**

**E 8,4 not more than 250 minutes**

**F 8,0 Not more than 240 minutes**

Wilcoxon test values (Z) and reached statistical significance (p) are presented in Table 9.

Table 9

Value Wilcoxon test for pairwise comparison of visits D, E and F

<b><u>Statistic</u></b>	<b><u>comparing visits</u></b>		
	<u>E - D</u>	<u>F - D</u>	<u>F - E</u>
<b><u>Value Wilcoxon test (Z)</u></b>	<u>-0,816</u>	<u>-0,272</u>	<u>-1,414</u>

<b><u>Level of statistical significance (p)</u></b>	<u>0,414</u>	<u>0,785</u>	<u>0,157</u>
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**Statistic comparing visits**

**E - D F - D F - E**

**Value Wilcoxon test (Z) -0,816 -0,272 -1,414**

**Level of statistical significance (p) 0,414 0,785 0,157**

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Discussion of the results

Evaluated was the influence of the drug Enterosgel® on absorption of alcohol in the blood.

It should be noted that in most cases exogenous toxins absorbed in the intestinal mucosa are available for the action of the sorbent from the moment of poisoning. This period depends on the form in which they are used (tablets, capsules, suspension) and the capacity of the absorber [4, 6]. This is why the study design has been standardized in a maximum of ingestion patients and selection of parameters for the body mass index and was designed so that it could be possible to

evaluate the efficiency of detoxification of the drug when taken at 60 min and 120 min after ingestion of ethanol.

When evaluating the speed of reduction of the concentration of ethanol in breath as a result of the analysis of data obtained during the execution of visits A, B and C ( 100 ml intake of a strong alcoholic drink), a statistically confirmed effect of the study drug was not found, but there was a trend towards more rapid decrease in the concentration of alcohol in the breath while taking the drug Enterosgel® to 3<sup>rd</sup> hour from the moment of reception of alcohol . No statistically significant differences between visits A, B and C in relation to the subjective duration of sobriety was marked, but the tendency to accelerate sobering against the backdrop of the study drug was evident.

In assessing the rate of decline in the concentration of ethanol in exhaled air as a result of analysis of data obtained in the course of visits D, E and F (200 ml intake of strong alcoholic drink), statistically significant differences between visits were found out, confirming the effect of the study drug, which manifests itself more rapid reduction of the concentration of ethanol in exhaled air against Enterosgel® dosing compared to control monitoring, and

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the most pronounced effect was observed in the study drug period from 2.5 to 5.5 hours from alcohol intake. While no statistically significant differences between visits in respect to subjective duration of sobering at visits D, E and F has been received.

It should be noted that the study drug being taken 1-2 hours after alcohol, has an effect at high doses of alcohol taken. This fact can be explained by the fact that large doses of alcohol absorption in the gastrointestinal tract require a certain time, and if the drug Enterosgel® gets into the gastrointestinal tract during this period, it exerts its effect on sorption of the liquor in the

digestive tract. Same small dose of alcohol is absorbed faster and does not have time to "get " under the effects of the studied enterosorbent .

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### **Conclusion**

Drug Enterosgel® at a dose of 45 g did not show statistically proven impact on the dynamics of the amount of ethanol vapor in the breath after drinking a strong alcoholic drink ( whiskey Jameson 40%) in 100 ml while taking the drug after 60 min and 120 min after drinking alcohol but there was a trend to a more rapid decrease in the concentration of alcohol in the breath while

taking the drug Enterosgel® by 3<sup>rd</sup> hour from the moment of reception of alcohol. Proven effect of the study drug was detected in case of the use of strong alcoholic drink ( whiskey *Jameson* 40%) 200 ml. Subjective sensation of sobering speed did not change in patients receiving the study drug.

Thus, the drug Enterosgel® at a dose of 45 g has an impact on the dynamics of amount of ethanol vapor in expired air after administration of a strong alcoholic drink, which manifests itself as a more pronounced decrease in the amount of ethanol vapor in exhaled air over time. The effect has been identified while taking the drug both after 60 min and 120 min after drinking.

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### **Conclusions**

1. Receiving Enterosgel Medical device® dose of 45 g (2 standard doses.) accelerates the decrease of blood ethanol level after administration of a strong alcoholic beverage.

2. Effect of the drug Enterosgel® taken depends on the amount of alcoholic drink: the larger the volume of alcohol taken, the more the pronounced the effect of the drug.

3. Effect of the drug Enterosgel® depends on the time of its administration, the earlier the drug is accepted, the more is the pronounced effect of its intake.

Principal investigator,

Head of Department

Internal Medicine propaedeutics

SZGMU named after I.I. Mechnikov

Honored scientist of the Russian Federation, Ph.D., professor E.I. Tkachenko

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### **List of References**

1. Bradberry S.M., Vale J.A. Multiple-dose activated charcoal: a review of relevant clinical studies / SM Bradberry, J.A. Vale // J.Toxicol. Clin. Toxicol. - 1995 . - № 5 , Vol.33. - P.407-416.

2. Casdorph H.R. Hypercholesteremia. Treatment with cholestyramine, a bile acid sequestering resin / HR Casdorph // Calif. Med. - 1967 . - № 4 , Vol.106. - P.293- 295.
3. Dillon E.C. Jr., Wilton J.H., Barlow J.C. et al. Large surface area activated charcoal and the inhibition of aspirin absorption / EC Dillon et al. // Ann. Emerg. Med. - 1989 . - № 5 , Vol.18. - P.547- 552.
4. Heimer G.M., Englund D.E. Enterohepatic recirculation of oestriol: inhibition by activated charcoal / GM Heimer, D.E. Englund // Acta Endocrinol. (Copenh). - 1986 . - № 1 , Vol.113. - P.93- 95.
5. Nikolaev V.G. Enterosorption / V.G. Nikolaev // Proceedings of the Fifth Int. Symp. on Hemoperfusion and Artificial Organs / Eds. TMS Chang, H. Bing-Lin. - Tianjin: China Academic Publishers, 1984 . - P.87- 99.
6. Nikolaev V.G. Peroral Application of synthetic activated charcoal in USSR / VG Nikolaev // Biomat., Art. Cells, Art. Org. - 1990 . - № 4 , Vol.18. - P.555- 568.
7. Remmert H.P., Olling M., Slob W. et al. Comparative antidotal efficacy of activated charcoal tablets, capsules and suspension in healthy volunteers / HP Remmert et al. // Eur. J. Clin. Pharmacol. - 1990 . - № 5 , Vol.39. - P.501- 505.
8. Shevchenko Yu.N., Dushanin B.M., Yashina N.I. New silicon compounds - porous organosilicon matrices for technology and medicine / Yu.N. Shevchenko, B.M. Dushanin, N.I. Yashina // In "Silicon for the chemical industry", Sandefjord, Norway, in 1996 . - P.114- 116.

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Bardenshteyn LM, NP Gerasimov , Mozhginsky JB, NI Beglyankin Alcoholism , drug addiction , substance abuse : a tutorial M. GEOTAR Media , 2009 . - 64 .

10 . Bondarev EV Shtrygol SY, SB Leaky Enterosorbents application in medical practice / EV Bondarev , SJ Shtrygol , SB Leaky // Pharmacist . - 2008 . - № 13. - Pp. 45-49 .

11. Moiseyev VS , AA Shelepin Alcohol and heart disease : a guide . - M. : GEOTAR Media, 2009 . - 168 .

12. Murzin EA Rationale for the enterosorbents in the treatment of chronic allergic / EA Murzin // Suchasni drugs that tehnologii - 2013 . - № 2-3 (98-99). - P.50 -53 .

13. Nikolaev VG , arrows VV Korovin YF etc. The theoretical basis and practical application of the method enterosorption / VG Nikolaev, VV Strelko , YF Korovin and others // Sorption detoxification and immune methods in medicine : Proc. of reports . - Kharkiv , 1982. - P.112 -114 .

14. Nikolaev VG , St. Michael S., Gurin NM Modern chelators and their mechanisms of action / VG Nikolaev, SV St. Michael , NM Gurin // Efferent therapy . - 2005 . - № 4 . - S. 3-17 .

15. Popov VD Sobko IV, IM Samodumova Efficiency as polymethylsiloxane hemosorbent experiments with obstructive jaundice / VD Popov , IV Sobko IM Samodumova // Clin. hir . - 1997 . - № 7-8. - P.87 .

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Appendix 1

Name of the patient \_\_\_\_\_

| Visit \_\_\_\_\_

| Time \_\_\_\_\_

| Visual analogue scale (VAS)

| Please mark vertical line how that assesses the degree of your intoxication on this scale from 0 to 10.

| Medical investigator \_\_\_\_\_ / \_\_\_\_\_  
| (name) /

|

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