The influence of Carbowhite, a modern silicon earth enterosorbent, on microhaemodynamics in patients with chronic toxic hepatitis associated with chronic obstructive pulmonary disease

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Key words: chronic toxic hepatitis, chronic obstructive pulmonary disease, enterosorbent, treatment

Introduction. In the recent years, there has been an increasing attention to associated (comorbid) internal disease in the research community, including that in digestive system problems, currently found in 60–80% patients with chronic disease [14, 15]. Current clinical and epidemiological studies indicate a significant increase in chronic hepatobiliary disease, primarily in chronic toxic hepatitis (CTH) in Ukraine and in other countries of CIS [3, 5, 11, 16, 17]. Our internal clinical experience (consistent with multiple reports from the research community), in a fraction of patients, CTH is associated with chronic bronchopulmonary disease, including chronic obstructive pulmonary disease (COPD). Repeated occurrences of COPD adversely affect the liver and may facilitate the progression of hepatic parenchymal disease with ultimate development of hepatic cirrhosis [5, 17]; in turn, a long history of chronic hepatic disease leads to deterioration of bronchopulmonary function (manifest as mutual aggravation).

A key role in the pathogenesis of chronic hepatic and bronchopulmonary conditions is played by impaired microcirculation, which reduces arterial perfusion of organs and tissues, including the liver [9]. Prolonged persistence of impaired microhaemodynamics leads to progressing metabolic abnormalities and triggers lipid peroxidation [9, 12, 17]. As a result, free radicals and peroxide compounds increase in blood and in other body fluids and oxidative damage to cellular and sub-cellular biomembranes increases. Therefore using antioxidant products simultaneously capable of improving microcirculation is an expedient and promising option.

Throughout many years, we have been analysing the comparative efficacy of various therapeutic approaches in patients with associations of hepatobiliary and bronchopulmonary disease. Our attention has been drawn to the feasibility of using enterosorbents in such patients, which contribute to improving immune and metabolic processes in the body as well as improving hepatic functions, as emphasized by other authors as well [4, 10]. An important place among sorbents belongs to silicon oxide-based products. Our attention has been drawn to the feasibility of using Carbowhite, a modern silicon earth enterosorbent, as a part of treatment plan in patients with CTH in the setting of COPD due to its potential influence on microhaemodynamics in patients with CTH in the setting of COPD.

Relationship of the work to academic programs, plans and themes. The research has been performed according to the Main Plan of Research and Development Activity (R&D) of the State Institution Lugansk State Medical University, which is a fragment of the following R&D topic: "Optimisation of out-patient treatment of chronic toxic hepatitis, associated with chronic obstructive pulmonary disease" (State Registration No 0113U005411).

The aim of the work is to study the influence of Carbowhite, a modern silicon earth enterosorbent, on the microhaemodynamic parameters in patients with CTH in the setting of COPD.

Materials and methods of the study.

The study enrolled 152 patients with CTH in the setting of COPD; there were 94 (61.8%) males and 58 (38.2%) females aged from 35 to 60 years. The history of CTH was from 2 to 20 years; the history of COPD was from 2 to 24 years. Patients with CTH in the setting of COPD were randomized into two groups by age, gender, the frequency of exacerbation of the chronic process in the liver and the severity of COPD, the main group (78 subjects) and the reference group (74 subjects). The diagnosis of hepatobiliary disease was made with review of history, clinical and laboratory (biochemical) tests of liver function and the findings of abdominal ultrasonography. The viral aetiology of chronic liver damage has been excluded in all

study subjects with blood enzyme immunoassay (ELISA) for markers of viral hepatitis.

The treatment of study subjects has been performed according to “Standardized protocols for diagnosis and treatment of digestive system disease” (The Order of the Ministry of Health of Ukraine No 271 dated 13.06.2005). In addition to those treatments, the main group of patients with CTH in the setting of COPD has additionally received the “Carbowhite” enterosorbent 3–4 tablets 2–3 times a day for 10–12 consecutive days.

The silicone earth enterosorbent “Carbowhite” possesses a number of positive pharmacological effects, which determines a wide range of its applications in various disease [1, 2]. Such positive pharmacological properties primarily include the high sorption capacity concerning microorganisms and toxins, the option to take moderate therapeutic doses of the enterosorbent due to a large active surface area and minimisation of micronutrient loss [8]. Apart from sorption of microbial pathogens and their metabolic by-products and absorption of various toxic substances the Carbowhite enterosorbent is selectively absorbing bile pigments (bilirubin derivatives, cholesterol and free and bound bile acids), which contributes to significantly reduced toxic load on excretory organs (primarily the liver). This is a rationale for using this product as a part of multimodality therapy of hepatobiliary conditions [2, 8].

Routine laboratory tests included haematology and urinalysis and blood glucose test. To assess the functional condition of the liver [13] the following biochemical parameters have been assessed with standardised methods: total bilirubin and its fractions (direct and indirect), the levels of serum aminotransferases (ALT and AST) and thymol test.

As the main method to assess microhaemodynamics, we used biomicroscopy of bulbar conjunctiva (BMBC) using the SchL-2M slit lamp; morphometry of nail bed capillaries with an M-70A capillaroscope was used an additional method. We analysed the calibre and the path of microvessels, the presence of aneurysms and vascular glomeruli, arteriolo-venular ratio (AVR), the function of arteriolo-venular

anastomoses (AVA), the shape of capillary loops and their count per power field, the rate and the pattern of blood flow and the condition of extravascular zones [9]. When performing assessment of morphological changes of the microcirculatory bed (MCB), we calculated conjunctival indices (CI): those of vascular (CI_1), intravascular (CI_2) and extravascular (perivascular) (CI_3) abnormalities, as well as total conjunctival index (CI_{total}), using the following formula: $CI_{total}= CI_1+CI_2+CI_3$ [9].

Statistical processing of study findings has been performed on an Intel Pentium Core Duo PC using one-way analysis of variance (ANOVA) and multivariate analysis of variance (licensed software packages Microsoft Office 2000, Microsoft Excel Stadia 6.1/prof and Statistica, XLSTAT-Pro for MS Excel, Statistical Package for Social Science) [7]. At this, we have taken into account the main principles of using statistical methods in clinical trials of medicinal products [6].

Results and discussion.

The analysis of morphological and functional parameters of MCB has demonstrated that already before the start of therapeutic interventions the patients of both groups under observation were found to have impaired microcirculation that affected all sections of MCB, namely vascular, intravascular and paravasal. The BMBC assessment has demonstrated a generalised arteriolar spasm, frequently accompanied by venular dilation, uneven calibre of venules and a meander-type tortuosity. Microscopic aneurysms were also found in the walls of microvessels (mainly in arterioles, less frequently in venules). In most patients with CTH in the setting of COPD, AVR was 1:4–1:5. Very typical features were polymorphic, torturous and deformed capillaries, as well as substantial decrease in total amount of functioning capillaries with quite broad avascular zones formed as a result. In both the main study group and in the reference study group, the patients with CTH in the setting of COPD also had reticular vascular structure. This pointed to functioning arteriolo-venular anastomoses, which partially shunted the blood directly from arterioles into venules, bypassing the capillary bed. Simultaneous detection of capillary/venular deformation and a substantial quantity of vascular glomeruli was a

sign of substantial morphological abnormalities of MCB in patients with CTH in the setting of COPD.

Using the BMBC method also allowed detection of clearly pronounced intravascular changes that have characterised blood flow in patients assessed. These changes were characterised by decelerated blood flow to the point of stasis in individual microscopic vessels (more frequently venules) in the setting of Stage II-III sludge syndrome in the venules, manifest as granular blood flow in these vessels. A number of patients with CTH in the setting of COPD had more pronounced microhaemodynamic abnormalities, characterised by Stage III-IV sludge syndrome present not only in the venules, but also in capillaries and arterioles, that is, in all types of microscopic vessels, which was manifest as total aggregation of blood cells in all segments of MCB. Thus, during BMBC in patients with CTH in the setting of COPD, we observed various degrees of intravascular abnormalities, from deceleration of blood flow to its complete arrest (stasis). It is noteworthy that in a number of cases there abnormalities of microcirculation were more substantial and manifested as retrograde blood flow in venules and capillaries. This indicated quite pronounced abnormalities of microhaemodynamics in patients with CTH in the setting of COPD.

Extravascular (paravascular) abnormalities of MCB in patients with CTH in the setting of COPD were manifest as substantial perivascular oedema of various degrees, as well as by frequent microhaemorrhages and pigmented spots in perivascular zones. The presence of pigmented spots of various colours (from dark grey to brownish-yellow) in study subjects was indicative of a quite prolonged persistence of MCB abnormalities and, as a result, of certain development of impaired microcirculation, since these pigmented spots appear at sites of previous microhaemorrhages.

The morphometry of nail bed capillaries in patients with CTH in the setting of COPD has detected pronounced abnormalities generally characterised by pale and opalescent background and insufficient visibility of capillary loops due to a pronounced peri-capillary oedema. The number of visible capillary loops in the

power filed has substantially decreased, which was manifest of decreased counts of functioning capillaries. Other capillaries have also undergone changes; due to deformation, they had various shapes (tortuous, comma/point-shaped and eight-shaped). Only “shades” of capillary were frequently seen due to desertion and absent blood flow. A number of patients were also found to have pendulous blood flow and retrograde blood flow in individual microvessels, which was evident of deep microhaemodynamic abnormalities.

Thus, both BMBC and morphometry of nail bed capillaries have demonstrated pronounced microcirculatory abnormalities, which embrace all portions of MCB (vascular, extravascular [paravascular] and intravascular).

Prior to the onset of treatment, patients with CTH in the setting of COPD in the main group and in the reference group were found to have CI significantly above normal (see Table 1).

Table 1

Conjunctival indices in patients with CTH in the setting of COPD before treatment (M±m)

Conjunctival index, (CI)	**Healthy subjects (n=30)**	**Groups of patients**		**p**
		Main group (n=78)	**Reference group (n=74)**	
CI_1	2.20±0.14	8.24±0.19***	8.20±0.21***	<0.05
CI_2	1.20±0.18	3.24±0.07***	3.21±0.05***	<0.05
CI_3	0.10±0.01	1.45±0.09***	1.42±0.08***	<0.05
CI_{total}	3.5±0.2	12.93±0.4***	12.83±0.4***	<0.05

Notes: in this table, the probability of difference in parameters has been calculated between the value in a particular group and normal values at $p<0.001$ — ***; the p column reflects the statistical significance of differences between the indices in the main group and in the reference group.

Table 1 demonstrates, that prior to therapeutic interventions the value of CI_1 in patients of the main group was on the average 3.75 times above normal ($p<0.001$); the same value in the patients of the reference group was 3.72 times above normal ($p<0.001$). This indicated pronounced vascular abnormalities before treatment in patients with CTH in the setting of COPD. Simultaneously, there was a substantial increase in average CI_2: 2.7-fold in the main group and 2.6-fold in the reference group ($p<0.001$). Such a significant increase in CI_2 indicates substantial intravascular abnormalities in patients with CTH in the setting of COPD concerning the immediate condition of blood flow. Mean pre-treatment CI_3 ratio was also elevated: 14.5-fold in patients of the main group ($p<0.001$) and 14.2-fold ($p<0.001$) in patients of the reference group in comparison to normal range. Finally, the mean integral parameter (CI_{total}) pre-treatment was above normal 3.69 times in patients of the main group ($p<0.001$) and 3.67 times in patients of the reference group ($p<0.001$). The data obtained are indicative of pronounced microcirculation abnormalities (both morphological and functional) in patients with CTH in the setting of COPD.

Repeated BMBC have demonstrated that in course of treatment the patients of the main group (those additionally receiving Carbowhite enterosorbent) had a distinctive trend towards normalisation of MCB, including decreased AVR, elimination of avascular zones and reticular structure of the vessels, acceleration of blood flow and relief of blood stasis, elimination of sludge syndrome in arterioles and capillaries and elimination of perivascular oedema. These patients had their microscopic haemorrhages undergo gradual resorption; overall, microcirculation improved (as evidenced by CI counts).

The analysis of data in Table 2 indeed demonstrates that all investigational CI values have reversed to the upper limit of normal ($P>0.05$) in the main group of patients. This indicates a substantial improvement of microcirculation in study subjects with CTH in the setting of COPD during treatment after inclusion of Carbowhite enterosorbent to the treatment protocol. The patients in the reference group, which received only conventional treatments, had persisting and more pronounced MCB changes, which reflects retained CI elevations. Thus, CI_1 in the

reference group was 4.45±0.17 points on the average, which was 2.02 times above normal ($p<0.001$); CI_2 was within 1.94±0.09 points, which was 1.61 times above normal ($p<0.001$); CI_3 value in patients under observation was 0.36±0.08 points on the average, which was 3.6 times normal for this parameter ($p<0.001$). Finally, the integral index of CI_{total} in this period of assessment was within 6.75±0.3 points on the average, which was 1.93 times above the relevant normal value ($p<0.001$).

Table 2

Conjunctival indices in patients with CTH in the setting of COPD post-treatment (M±m)

Conjunctival indices (CI)	Healthy subjects (n=30)	Groups of patients		p
		Main group (n=78)	Reference group (n=74)	
CI_1	2.20±0.14	2.21±0.16	4.45±0.17***	<0.001
CI_2	1.20±0.18	1.22±0.07	1.94±0.09***	<0.001
CI_3	0.10±0.01	0.11±0.02	0.36±0.08***	<0.001
CI_{total}	3.5±0.2	3.54±0.2	6.75±0.3***	<0.001

Notes: in the above table, the probability of differences of values has been calculated between the respective value in the group and normal value at $p<0.001$ — ***; the p column reflects the probability of differences between the parameters in the main group and in the reference group.

Identical data were obtained in morphometry of nail bed capillaries. In course of treatment, the patients of the main group had gradually diminishing paleness of opalescence of the background, increasing numbers of functional capillary loops per power field and improving visibility of the latter, normalising capillary shapes and calibres and substantially accelerating blood flow. In the reference group, the patients with CTH in the setting of COPD by the end of treatment in most cases had retain arteriolar spasm, dilation and uneven calibres of the venules and abnormal arteriolo-venular ratios; the microvessels Stage I–II had sludge syndrome, perivascular

oedema, and in a number of cases there were fresh microscopic haemorrhages. It was noteworthy that the patients had persisting morphological microvascular abnormalities manifest as deformities, microscopic aneurysms and significant numbers of avascular zones, characterized by reticular structure of microvessels. The morphometry of nail bed capillaries has also revealed MCB abnormalities in patients of the reference group. The patients of the reference group had opalescent and pale capillaroscopic background, substantial numbers of non-functional capillaries (capillary "shadows") and poor visibility of capillaries due to a pronounced peri-capillary oedema The functional capillaries remained deformed, frequently seen as points, commas, and, more typically, eight-shapes, which indicated a substantial tortuosity of capillaries seen as double loops. Thus, on completion of traditional therapy, the patients with CTH in the setting of COPD continued to have morphological and functional shifts of microhaemodynamics.

Therefore, in terms of pathogenesis, inclusion of Carbowhite enterosorbent to the therapeutic schedule in patients with CTH in the setting of COPD facilitates full restoration of functional and morphological parameters of microcirculation. The results of the study allow us to assert that inclusion of Carbowhite enterosorbent to therapeutic plans for patients with exacerbations of chronic hepatic toxic disease has a strong pathogenetical rationale, which allows recommending this combination for multimodality therapy of patients with the above comorbidities.

Conclusions

1. The patients with CTH in the setting of COPD had clearly pronounced morphological and functional abnormalities of microcirculation manifest as generalized arteriolar spasm, tortuosity and irregular calibres of venules and capillaries, reduced numbers of functioning capillaries with avascular zones, reticular structure of microscopic vessels (considered to be a sign of functional arteriolo-venular anastomoses), decreased arteriolo-venular ratios; deceleration of blood flow in microscopic vessels and evidences of sludge syndrome in venules and capillaries. The morphometry of nail bed capillaries (capillaroscopy) has demonstrated paleness of opalescence of the background,

decreasing numbers of functional capillary loops per power field, distorted shapes of the capillaries and deceleration of capillary blood flow to the point of arrest in a number of microscopic vessels).

2. Inclusion of Carbowhite, a modern silicon earth enterosorbent to the treatment protocol in patients with CTH in the setting of COPD improves microcirculation and eliminates morphologic and functional abnormalities of MCB. Thus, in the main group of patients (receiving Carbowhite enterosorbent) all investigational parameters of microhaemodynamics (CI) have decreased to the upper limit of normal after the main course of treatment, which was evident of substantial improvement of microcirculation in study subjects.
3. When only conventional therapies were used (patients of the reference group), there also were positive changes of investigational parameters of circulation (albeit less pronounced); no complete elimination of MCB abnormalities was found, which is evident of retained chronic inflammatory process in the liver and requires further medical rehabilitation of the patients.
4. That being said, integration of the modern silicone earth enterosorbent Carbowhite into therapeutic schedules can be considered to have a substantial pathogenetic basis; the product can be recommended for use in treatment protocols for patients with CTH in the setting of COPD.

References

1. «Біле вугілля 400». добавка дієтична. — Київ : ТОВ «Омніфарма Київ», 2008.

2. Біле вугілля. Режим доступу: www.omnifarma.kiev.ua

3. Буеверов А. О. Лекарственный гепатит: если препарат нельзя отменить / А. О. Буеверов // Клин. перспективы гастроэнтерологии и гепатологии. — 2007. — № 5. — С. 13–19.

4. Вершинин А. С. Энтеросорбция в практике семейного врача / А. С. Вершинин, А. Н. Попилов // Русский медицинский журнал. — 2008. — № 4. — С. 166–170.

5. Дрель В. Ф. Морфологические проявления портального цирроза печени при моделировании токсического гепатита / В. Ф. Дрель, А. А. Виноградов // Український морфологічний альманах. — 2013. — Т 11, No 1. — С. 109–111.

6. Лапач С. Н. Основные принципы применения статистических методов в клинических испытаниях / С. Н. Лапач, А. В. Чубенко, П. Н. Бабич. — Киев : Морион, 2002. — 160 с.

7. Лапач С. Н. Статистические методы в медико-биологических исследованиях с использованием Excel / С. Н. Лапач, А. В. Чубенко, П. Н. Бабич. — Киев : Морион, 2000. — 320 с.

8. Медицинская химия и медицинское применение диоксида кремния / Под ред. А. А. Чуйко. — Киев : Наукова думка, 2003. — 416 с.

9. Мчедлишвили Г. И. Микроциркуляция крови: общие закономерности регулирования и нарушений / Г. И. Мчедлишвили. — Л. : Наука, 1989. — 295 с.

10. Полий И. Г. Роль энтеросорбции в лечении заболеваний печени / И. Г. Полий // Новости медицины и фармации. — 2008. — № 4. — С. 16–17.

11. Попова Ю. С. Болезни печени и желчного пузыря. Диагностика, лечение, профилактика / Ю. С. Попова. — СПб. : изд-во «Крылов», 2008. — 192 с.

12. Селезнев С. А. Клинические аспекты микрогемоциркуляции / С. А. Селезнев, Т. И. Назаренко, В. С. Зайцев. — Л. : Медицина, 1985. — 208 с.

13. Унифицированные биохимические методы обследования больных: методические рекомендации // Под. ред. Л. Л. Громашевской. — Киев : МЗ Украины, 1990. — 64 с.

14. Філіппов Ю. О. Основні показники гастроентерологічної захворюваності в Україні / Ю. О. Філіппов, І. Ю. Скирда, Л. М. Петречук // Гастроентерологія : міжвід. зб. — Дніпропетровськ, 2006. — Вип. 37. — С. 3–9.

15. Elshtein N. Polymorbidity in gastroenterological practice / N. Elshtein // Acta Medico. — 2006. — Vol. 5. — P. 70–73.

16. Lee W. M. Recognizing drug-induced liver injury: current problems, possible solutions / W. M. Lee, J. R. Senior // Toxicol. Pathol. — 2012. — Vol. 33. — P. 155–164.

17. Park B. K. The role of metabolic activation in drug-induced hepatotoxicity / B. K. Park, N. R. Kitteringham, J. L. Maggs // Annu. Rev. Pharmacol. Toxicol. — 2014. — Vol. 45. — P. 177–202.

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The influence of Carbowhite, a modern silicon earth enterosorbent, on microhaemodynamics in patients with chronic toxic hepatitis associated with chronic obstructive pulmonary disease, was studied. Thus detected that aplication of sorbent provided normalisation of morphological and functional indexes of this microhaemodinamic promotes for the inspected patients.