EFFECT OF SODIUM BICARBONATE ON THE DEVELOPMENT OF GASTRIC STASIS IN THE RAT MODEL OF MYELOABLATIVE CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE

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Myeloablative cytostatic therapy is often associated with gastrointestinal (GI) stasis that is a component of pathogenesis of the bacterial overgrowth syndrome, endotoxicosis, systemic inflammation, sepsis, emetic syndrome. The study was aimed to test the hypothesis that sodium bicarbonate ($NaHCO_3$), the alkalinizing agent administrated by gavage in the rat model of myeloablative cytostatic therapy with cyclophosphamide (CP), would have a protective effect against GI stasis. We assessed the effects of intragastric $NaHCO_3$ administrations on the development of GI stasis, acute chemotherapy-induced mucositis of the small intestine, and urinary excretion of indican using 140 Wistar rats with the body weight of 161–190 g as a model of myeloablative cytostatic therapy with the intravenously injected CP. The CP administration in a dose of 390 mg/kg resulted in dystrophic changes in the small intestinal mucosa, the development of GI stasis with predominant gastric stasis within the first 24 h, and the increase in excretion of indican. Intragastric administration of $NaHCO_3$ in a dose equivalent to 350 mL of the 4% $NaHCO_3$ solution in humans to rats 30 min before and immediately after the CP administration prevented acute chemotherapy-induced mucositis of the small intestine and alleviated the symptoms of gastric stasis and excessive growth of the indole-producing gastrointestinal microbiota. The reported approach to emergency drug prevention of the myeloablative cytostatic drug therapy gastrointestinal complications holds promise for testing of the use of CP and other alkylating drugs as cytostatic agents.

Keywords: cyclophosphamide, myeloablative cytostatic therapy, rat model, acute cytostatic mucositis, gastric stasis, indican, sodium bicarbonate

Author contribution: Vakunenkova OA — experimental study; Ivnitsky JuJu — rationale, developing the experimental model, data interpretation and discussion; Gaykova ON — morphometry data interpretation; Kozlov AA — morphometry studies; Schäfer TV — experimental procedure, data processing and visualization, developing the experimental model. All authors contributed to discussion, manuscript writing and editing.

Compliance with ethical standards: the study was carried out in accordance with the principles of bioethics, approved by the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes.

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ВЛИЯНИЕ ГИДРОКАРБОНАТА НАТРИЯ НА ФОРМИРОВАНИЕ ГАСТРОСТАЗА У КРЫС ПРИ МОДЕЛИРОВАНИИ МИЕЛОАБЛЯЦИОННОЙ ХИМИОТЕРАПИИ ЦИКЛОФОСФАНОМ

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При миелоабляционной цитостатической терапии нередко возникает желудочно-кишечный стаз (ЖКС) — звено патогенеза синдрома избыточного бактериального роста, эндотоксикоза, системного воспаления, сепсиса, эметического синдрома. Целью исследования было проверить гипотезу о том, что ощелачивающий агент гидрокарбонат натрия ($NaHCO_3$), вводимый в желудок при моделировании на крысах миелоабляционной цитостатической терапии циклофосфаном (ЦФ), проявит профилактическую активность в отношении ЖКС. Изучали влияние вводимого в желудок $NaHCO_3$ на формирование желудочно-кишечного стаза, острого цитостатического мукозита тонкой кишки и экскрецию индикана с мочой при моделировании на 140 крысах линии Вистар массой тела 161–190 г миелоабляционной цитостатической терапии внутривенным введением ЦФ. Введение ЦФ в дозе 390 мг/кг вело к дистрофическим изменениям в слизистой оболочке тонкой кишки, развитию в течение ближайших суток ЖКС с преобладанием гастростаза и повышению экскреции индикана. Введение за 30 мин до и тотчас после ЦФ в желудок крыс $NaHCO_3$ в дозе, эквивалентной 350 мл его 4%-го раствора для человека, предупреждало формирование острого цитостатического мукозита тонкой кишки, смягчало проявления гастростаза и избыточного роста индол-продуцирующей желудочно-кишечной микрофлоры. Представленный подход к экстренной медикаментозной профилактике желудочно-кишечных осложнений миелоабляционной цитостатической фармакотерапии перспективен для апробации при использовании в качестве цитостатического агента не только ЦФ, но и других медикаментозных средств алкилирующего действия.

Ключевые слова: циклофосфан, миелоабляционная цитостатическая терапия, крысы, острый цитостатический мукозит, гастростаз, индикан, гидрокарбонат натрия

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Соблюдение этических стандартов: исследование проведено с соблюдением правил биоэтики, утвержденных Европейской конвенцией о защите позвоночных животных, используемых для экспериментальных и других целей.

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The previously reported study revealed retention of the X-ray shadow of barium sulfate administrated into the rat's stomach that was associated with acute cyclophosphamide toxicity [1] and was typical for gastrointestinal (GI) stasis. This potentially fatal complication often occurs during the patient's preparation for hematopoietic stem cell transplantation, myeloablative cytostatic conditioning [2]; in some recipients, the X-ray gastric shadow spreads to large parts of both abdominal and thoracic cavities [3]. The GI stasis clinical significance results from its negative impact on the chemotherapy outcome. GI stasis hampers the patients' feeding, makes it pointless to prescribe oral medications; intestinal bacterial overgrowth that is associated with GI stasis results in realization of quorum sensing [4], enhanced production of toxic substances by bacteria, as well as in endotoxemia and endotoxicosis. GI stasis contributes to the intestinal barrier damage associated with the Gram-negative bacterial lipopolysaccharide release into the bloodstream, systemic inflammation [5] and sepsis [6]. GI stasis is involved in the pathogenesis of delayed chemotherapy-induced vomiting; however, prescribing antiemetics [7, 8], prokinetics or antispasmodics [7] to such patients does not resolve the acute chemotherapy-induced gastrointestinal mucositis, a defensive response to the first stage of which is believed to be represented by GI stasis [9]. The use of enteroprotectors, i.e. medications capable of preventing acute gastrointestinal mucositis, seems to be a more promising approach to prevention of GI stasis associated with myeloablative conditioning. When using cytostatic therapy with cyclophosphamide (CP), enteroprotective effect can hypothetically be achieved by alkalinization of the chyme moving through the gastrointestinal tract. With increasing pH of biological media, spontaneous hydrolysis of the active CP metabolite produced in the liver is slowed down, accumulation of more toxic metabolites, acrolein and phosphoramide mustard, is inhibited [10], and toxicity of aldehyde dehydrogenase, the key enzyme responsible for the CP detoxification, the optimal pH value of which is within the alkaline range, is increased [11]. Higher normal pH values of the cytoplasm relative to the tumor cells contribute to the CP selective anticancer activity [12]. Acidification of the chyme by intragastric administration of weak acid solutions [13] or lactulose [14] increased the severity of acute cyclophosphamide toxicity in rats. Intragastric CP administration resulted in more severe GI stasis than intraperitoneal injection of the same dose, which could be partly due to more intense CP toxification in the acidic environment [1]. The study was aimed to test the hypothesis that $NaHCO_3$, the alkalinizing agent administrated by gavage in the rat model of myeloablative cytostatic therapy with cyclophosphamide, would have a protective effect against GI stasis.

METHODS

The study involved 140 male Wistar rats (161–190 g) obtained from the Rappolovo laboratory animal nursery. The animals were treated in accordance with the Principles of Good Laboratory Practice, stated in the Order № 708n of the Ministry of Health of the Russian Federation of 1 August 2010. The standard rat diet and ad libitum water access were provided. The animals were randomized into experimental groups. To deprive the rats of food, they were placed in the slatter floor cages (to avoid coprophagy and consumption of the bedding components) with access to water only for a specified time. Myeloablative cytostatic therapy was modeled by a single lateral tail vein injection of the freshly prepared aqueous solution of Endoxan (Baxter Oncology GmbH; Germany) in the amount of 10 mL/kg in a dose of 390 mg/kg (≈ 1.7 $LD_{99/30\ day}$), which was equivalent to the daily dosage for humans of 60 mg/kg used in the myeloablative conditioning regimens [15]. Laparotomy and organ harvesting were performed under the mask halothane anaesthesia. The GI stasis severity was assessed based on the relative weight of chyme in the stomach and caecum calculated as a difference between the weight of the organ filled with chyme and the empty organ (*gaster*, *caecum*) in grams relative to the body weight in kilograms.

During the first phase of the study we assessed the dynamics of the GI stasis development after the myeloablative conditioning. For that the animals were distributed into seven groups, among which the first one was represented by intact rats (n = 10) having unlimited access to food, another tree groups were deprived of food 4, 24 or 48 h after the CP administration, and the three remaining groups were deprived of food within the same time frame but did not receive CP (n = 10 in each group). All animals were subjected to laparotomy 72 h after the CP administration to assess the GI stasis severity.

During the second phase of the study we assessed the effects of $NaHCO_3$ on the GI stasis severity and the growth rate of gastrointestinal microbiota. For that the rats deprived of food between 24 and 72 h after the CP administration were used. The animals were distributed into five groups, among which the first one was represented by intact rats (n = 10), and all other groups were represented by the rats administered with CP (n = 10 in each group). Rats of the second groups were administered CP only; the 4% $NaHCO_3$ solution (pH = 8.34) in the amount of 15 mL/kg was administrated by gavage to rats in the third group 30 min before the CP administration. In the fourth group, administration of $NaHCO_3$ 30 min before CP was supplemented by the repeated administration of $NaHCO_3$ in the same dose after the CP injection; in the fifth group, $NaHCO_3$ was administrated by gavage four times: 30 min before, immediately after, 60 and 120 min after the CP administration. All the rats were placed in metabolic cages for urine collection 48 h after the CP injection; 50 μL of the 10% trichloroacetic acid solution per chamber were added to the urinal chambers as a preservative. The GI stasis severity was assessed 72 h after the CP administration. To assess selectivity of the $NaHCO_3$ protective effect, the relative weight of the spleen was measured along with the relative weight of the gaster and caecum chyme as a measure of chemotherapy-induced damage to the hemopoietic system. Urinary excretion of indican was used as a measure of the gastrointestinal microbiota growth rate [16]. The volume of urine sampled within 24 h was measured, and indican, an intestinal endotoxicosis indicator [17], the urinary excretion of which was measured in micrograms per kilogram of body weight per hour, was quantified.

During the third phase of the study we assessed morphological changes in the small intestine associated with the myeloablative cytostatic therapy modeling by the above method, as well as the effects of double $NaHCO_3$ administration into the stomach (30 min before and immediately after CP) on these changes. The 10 cm long small intestine sections (*duodenum* proximal of *pylorus*; *jejunum* 10 cm distal of *flexura duodenojejunalis*; *ileum* proximal of *caecum*) were fixed in 10% formalin and embedded in paraffin. The annular slices were stained with hematoxylin and eosin and then examined with the 3DHISTECH Pannoramic MIDI scanning digital microscope (Carl Zeiss AG; Germany). We enumerated intestinal villi and measured their length in 58–73 slices of each organ obtained from three animals; the results were processed using the Case Viewer application (3DHISTECH Ltd.; Hungary).

The results were presented as the mean and standard error of the mean (M ± *m*). The effects of the injected substances on the quantitative parameters were estimated by analysis of variance. When the resulting models were significant, the intergroup comparison of mean values was performed using the Tukey's honestly significant difference test [18]. Correlations between traits were represented as the Spearman's rank correlation coefficients (r_s). The α-value of 0.05 was considered to be a critical significance level.

RESULTS

Three days after the CP administration to rats deprived of food within 48 h before laparotomy, the dilated stomach that was filled with chyme occupied most of the abdominal cavity; it seemed to be empty in intact animals. The increase in the volume of the caecum associated with the CP administration was lower (Fig. 1). Food consumed within the first 24 h after the CP injection stayed in the stomach over the next 48 h. This resulted in the 7–13 fold gastric chyme relative weight increase. Excessive accumulation of chyme in the caecum was represented as a trend (p = 0.075 for the animals deprived of food for 4 h; Fig. 2). The body weight of animals administered with CP measured on the day of laparotomy made up a smaller share of body weight measured prior to exposure, than in controls: 78.9 ± 0.8% vs. 86.2 ± 0.5% ($p < 0.05$).

Administration of $NaHCO_3$ into the stomach 30 min before and immediately after the CP administration prevented GI stasis: the gastric chyme relative weight was on average 2.6 times lower, than in unprotected animals, however, it was still three times higher than in intact rats. The decrease in the relative weight of the caecal chyme was represented as a trend (p = 0.084). The four-time administration of $NaHCO_3$ had no benefit over the double administration, and a single preventive $NaHCO_3$ administration was ineffective. The $NaHCO_3$ administration had little effect on the CP-induced hypotrophy of the spleen (Fig. 3).

Urinary excretion of indican after the exposure to CP only was on average 1.9 times higher than in intact rats; the double intragastric $NaHCO_3$ administration resulted in the 1.4-fold increase, which manifested as a trend only (p = 0.067; Fig. 4). In the rats administered with CP, this indicator showed a strong negative correlation (r = –0.77; $p < 0.01$) with the body weight measured on a day of laparotomy as a percentage of body weight measured before the exposure. Excretion of indican in rats administered with CP only positively correlated with the relative weight of the caecal chyme (r = 0.66; $p < 0.05$); when $NaHCO_3$ was administered together with CP, the correlation was weak (r = 0.15).

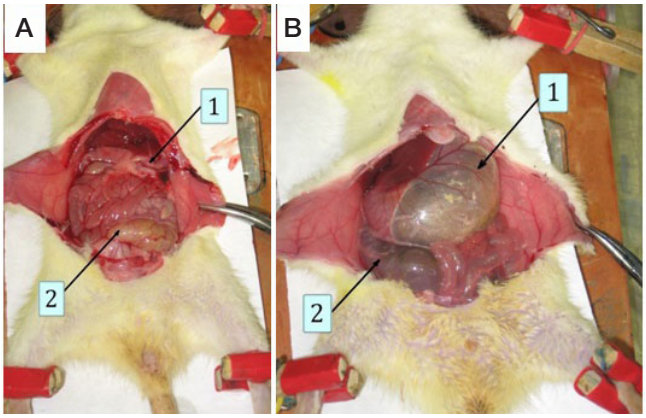

Fig. 1. Abdominal organs of the rats deprived of food 48 h before laparotomy: intact (**A**); 72 h after intravenous injection of cyclophosphamide in a dose of 390 mg/kg (**B**). *Arrows* show: 1 — stomach; 2 — caecum

Three days after the CP administration, the changes (congestion, inflammation, atrophy) were observed in the small intestine, the severity of which increased in the direction from the duodenum to the ileum. The average length of intestinal villi was reduced, and a downward trend in the number of villi was observed in the annular slices of the organ. Atrophy of villi was found in the ileum. No such alterations were found in rats administered with $NaHCO_3$ in addition to CP (Table; Fig. 5).

DISCUSSION

Modelling myeloablative cytostatic therapy in rats was associated with deep inhibition of the gastrointestinal (GI) tract propulsive function with predominance of gastric stasis developing during the first hours after the CP administration. The gastric transit time exceeded three days. It is 10–48 min in healthy people [19], that is why it can be assumed that gastric stasis persists in the recipients of hematopoietic stem cells for much of the myeloablative conditioning course lasting 3–5 days [15]. It is possible that gastric stasis is involved in general health deterioration during myeloablative cytostatic therapy, as indicated by the fact that the animals lose about a

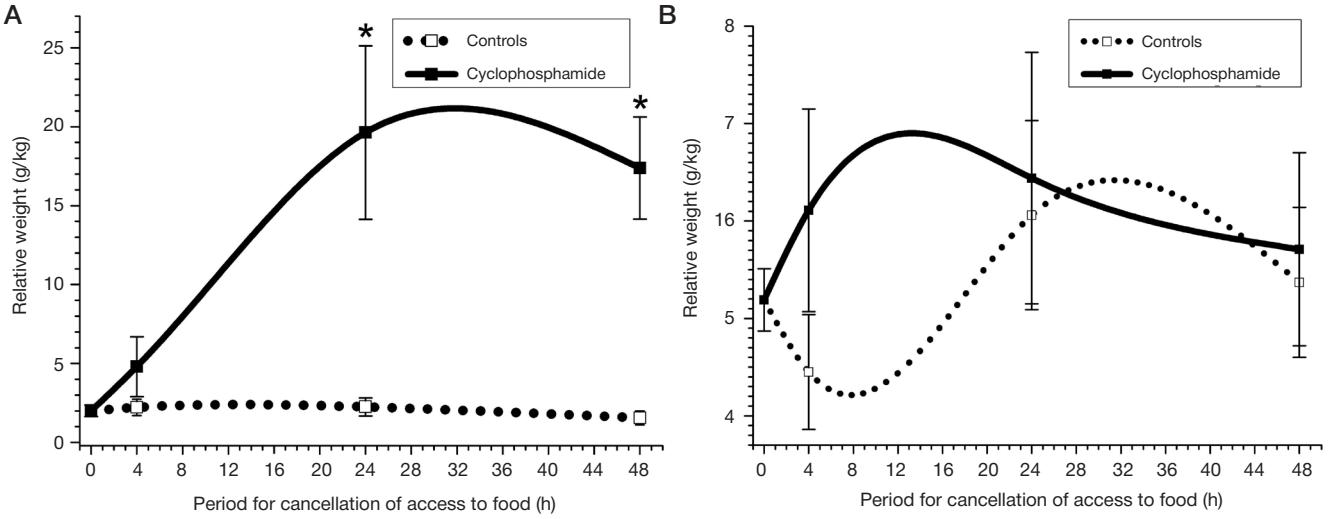

Fig. 2. Relative weight of the gastric (**A**) and caecal (**B**) chyme in rats 72 h after intravenous injection of cyclophosphamide in a dose of 390 mg/kg (M ± *m*; *n* = 10) depending on the time of access to food after the exposure. Controls — animals not administered with cyclophosphamide. At the beginning of the horizontal axis — values of the group of rats not administered with cyclophosphamide and having unlimited access to food. * — significant differences from controls ($p < 0.05$)

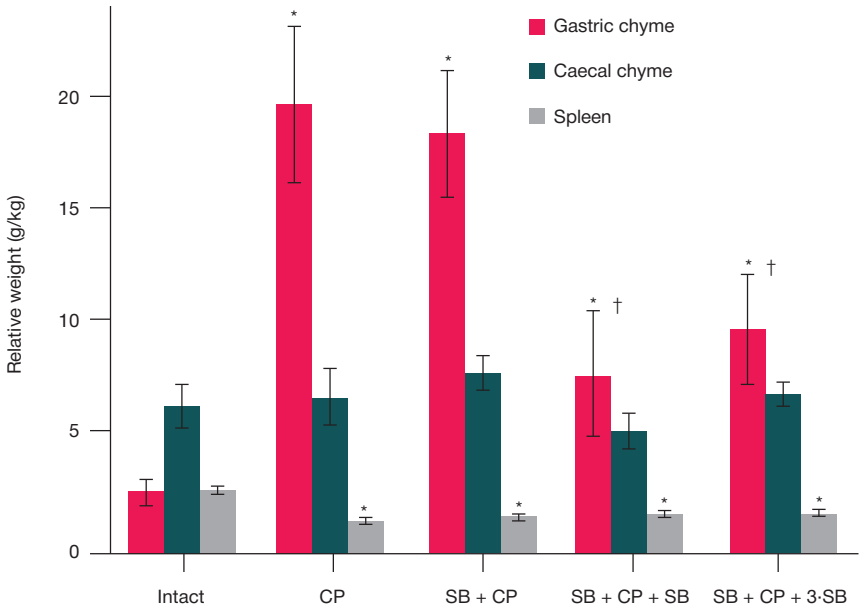

Fig. 3. Relative weight of the gastric chyme, caecal chyme and the spleen in rats 72 h after intravenous injection of cyclophosphamide in a dose of 390 mg/kg (M ± *m*; *n* = 10). "Intact" — rats not administered with drugs; "CP" — rats administered with cyclophosphamide only; "SB + CP" — rats that received intragastric administration of the 4% sodium bicarbonate solution 30 before the cyclophosphamide administration; "SB + CP + SB" — rats that received intragastric administration of the 4% sodium bicarbonate solution 30 before and immediately after the cyclophosphamide administration; "SB + CP + SB"— rats that received intragastric administration of the 4% sodium bicarbonate solution 30 before, immediately after, 1 and 2 h after the cyclophosphamide administration. All the animals were deprived of food 24 h after the cyclophosphamide administration. Significant differences ($p < 0.05$): * — from the intact group; † — from the "CP" and "$NaHCO_3$ + CP" groups

quarter of their initial body weight within three days after the CP administration.

Intragastric administration of two doses of $NaHCO_3$ to a total dose, which was equivalent to 350 mL of the 4% solution in humans, made it possible to a significant extent, although not completely, preserve the propulsive function of the stomach. $NaHCO_3$ was most effective during the period that did not exceed the CP $T_{½}$ after intravenous administration to rats, i.e. 0.5 h [20]. Consequently, inhibition of the CP toxification predominated in the mechanism underlying the $NaHCO_3$ protective effect. Because of the weakly alkaline nature of the $NaHCO_3$ solution and the salt's capability of being absorbed by the GI tract mucosa, the protective effect involved inhibition of the acrolein and phosphoramide mustard production in epithelial cells of the stomach and/or small intestine. This is also indicated by the $NaHCO_3$ inability to prevent the CP-induced hypotrophy of the spleen that can be explained by the buffering properties of blood not allowing one to ensure the comparable increase in pH of cells of the stem or proliferative pool of the hematopoietic system. Thus, the $NaHCO_3$ protective effect of the GI tract was selective, which was conductive to its testing in disorders requiring myeloablative cytostatic therapy.

The pH values that are optimal for the enzymes responsible for DNA repair are within the range close to neutral (6.5–7.5), that is why acidosis, that results from the shift from oxidative to glycolytic phosphorylation and comes along with mitochondrial damage caused by mustard agents [21], can violate DNA repair. Acidosis also leads to another effect that contributes to enterocytopenia: the expression of pro-apoptotic proteins that activate caspases [22]. This determines the possibility of the $NaHCO_3$ protective effects not only in acute poisoning with CP, but in poisoning with other alkylating cytostatic agents; the hypothesis needs further testing.

The CP-induced gastric stasis was associated with the increase in urinary excretion of indican (the indoxyl sulfate potassium salt), the end product of the liver metabolism of indole (oxidation to indoxyl and its sulfonation), the main source of which in experimental rats was represented by the reaction catalyzed by the gut microbiota tryptophanase. This indicates the increase in the weight and/or metabolic activity of intestinal microbiota, that produces indole but does not metabolize it, in GI stasis; in this case, a more intense production of both indole and another toxic product of the tryptophanase reaction, ammonia, in the GI tract is inevitable. The CP-induced increase in excretion of indican was lower that the increase in the relative weight of the gastric chyme, which was probably due to lower resorption capacity of the stomach compared to the intestine. When $NaHCO_3$ was administered, the differences in excretion of indican between the intact animals and the rats administered with CP were minor, which characterized the endotoxemia severity in the latter.

The myeloablative cytostatic therapy modeling was associated with damage to the small intestine. The severity of damage increased distally, as determined by the fact that the abundance of bacteria in the ileal chyme exceeded that in the duodenal chyme by four orders of magnitude [23]. This is consistent with the hypothesis that gastric stasis represents the

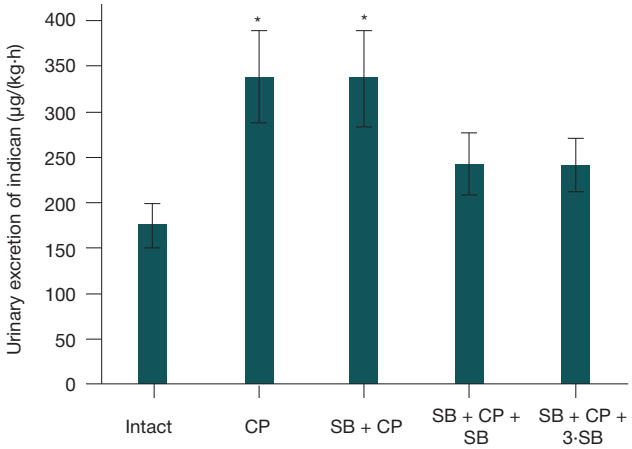

Fig. 4. Urinary excretion of indican in rats 72 h after intravenous injection of cyclophosphamide in a dose of 390 mg/kg (M ± *m*; *n* = 10). The symbols are the same as in Fig. 3

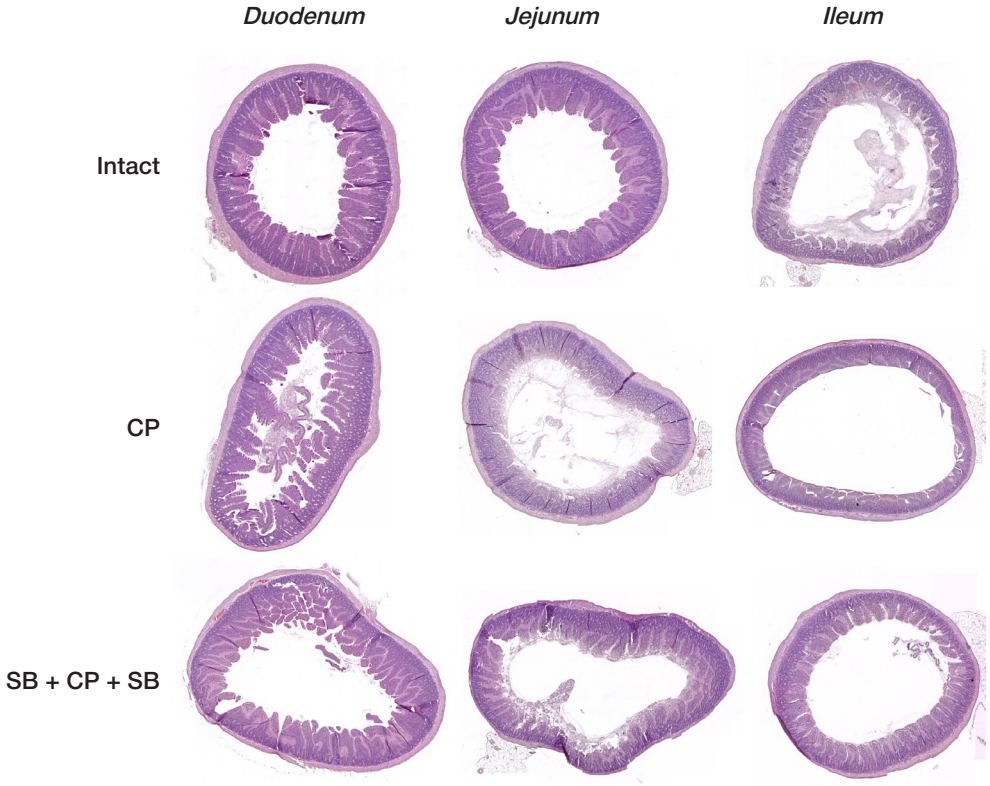

Fig. 5. Annular slices of the duodenum, jejunum, and ileum of the rats 72 h after intravenous injection of cyclophosphamide in a dose of 390 mg/kg

body's protective response, the biological meaning of which is to prevent injury of the small intestine damaged by the cytostatic agent, since the small intestine is a GI tract segment that is most sensitive to cytostatic agents [24]. The use of $NaHCO_3$ prevented dystrophic changes in all parts of the small intestine. As for duodenum and proximal jejunum, such an effect can be explained by local alkalinization, however, the $NaHCO_3$ protective effect on the ileum requires further investigation. This is due to the fact that the time it takes for the $NaHCO_3$ solution to reach it (at least 3 h according to preliminary data acquired by monitoring methylene blue administration in the rat stomach) far exceeds $T_{½}$ of CP administered to rats by intravenous injection [20].

The problem of acute chemotherapy-induced gastrointestinal mucositis treatment is far from being resolved. Antioxidants, anti-inflammatory agents and inhibitors of apoptosis are considered as possible therapeutic agents [25]. However, delivery of these agents to the GI tract segment most sensitive to cytostatic agents, the small intestine, is only achieved when there is no gastric stasis. That is why drug treatment should be preceded by the use of medications for emergency prevention of gastric stasis. The findings indicate potential benefits from early prescription of oral alkalinizing agents, such as sodium bicarbonate, for this purpose.

CONCLUSIONS

1) Single intravenous injection of cyclophosphamide in a dose equivalent to that used for myeloablative conditioning to rats results in dystrophic changes in the small intestinal mucosa, the

Table. Morphological signs of acute chemotherapy-induced gastrointestinal mucositis in rats 72 h after intravenous injection of cyclophosphamide in a dose of 390 mg/kg

Experimental group	Average number of villi, M ± *m*	Average villus length, M ± *m*, мкм	Main qualitative trait
Duodenum			
Intact	39.0 ± 2.9	366 ± 8	No
CP	34.5 ± 3.7	294 ± 9*	Hyperemia
$NaHCO_3$ + CP + $NaHCO_3$	40.1 ± 2.0	355 ± 10†	No
Jejunum			
Intact	31.5 ± 2.4	305 ± 7	No
CP	27.0 ± 3.6	208 ± 8*	Inflammation
$NaHCO_3$ + CP + $NaHCO_3$	35.0 ± 3.9	292 ± 5†	No
Ileum			
Intact	36.2 ± 2.5	230 ± 6	No
CP	No villi		Atrophy
$NaHCO_3$ + CP + $NaHCO_3$	43.0 ± 2.5	239 ± 5	No

Note: "Intact" — rats that received no drug treatment; "CP" — rats that received cyclophosphamide only; "$NaHCO_3$ + CP + $NaHCO_3$" — intragastric administration by oral gavage of 4% sodium bicarbonate solution 10 min before and immediately after the cyclophosphamide administration. Significant differences ($p < 0.05$): * — from the intact group; † — from the "CP" group.

development of gastrointestinal stasis with predominant gastric stasis within 24 h, and the excess growth of the indole-producing gastrointestinal microbiota. 2) Intragastric administration of sodium bicarbonate in a dose equivalent to 350 mL of 4% sodium bicarbonate solution in humans to rats 30 min before and immediately after the cyclophosphamide administration to a considerable extent prevents acute chemotherapy-induced gastrointestinal mucositis, gastric stasis, and the excess growth of gastrointestinal microbiota. 3) Early oral administration of sodium bicarbonate represents a promising approach to prevention of gastric stasis when performing myeloablative chemotherapy with cyclophosphamide; the approach enables further oral administration of drugs for treatment of acute chemotherapy-induced mucositis of the small intestine to patients. 4) Testing of the above approach to prevention of gastric stasis associated with myeloablative cytostatic therapy with cyclophosphamide and other alkylating cytostatic drugs is of interest.

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