# EFFECT OF SODIUM BICARBONATE OR HYDROCHLORIC ACID INTRAGASTRIC ADMINISTRATION ON GUT-DERIVED ENDOTOXEMIA IN RATS RECEIVING CYCLOPHOSPHAMIDE MYELOABLATIVE CONDITIONING

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Toxic effects of the myeloablative cyclophosphamide (CP) doses include damage to the gastrointestinal tract. This is manifested by gastrointestinal stasis, cytostatic drug-induced damage to the small intestinal mucosa, and acute gut-derived endotoxemia. The study was aimed to identify causal relationships between gastrointestinal stasis, enterocytopenia, and acute gut-derived endotoxemia in the rat model of the CP myeloablative conditioning. We assessed the effects of the intragastrically administered 0.48 M sodium bicarbonate ($NaHCO_3$) solution or the 0.1 M hydrochloric acid (HCl) solution on the indicators of gastrointestinal stasis, enterocytopenia, portal blood levels of endotoxin, ammonia, urea, and urinary indican excretion. The stomach overfilled with chyme, decreased alkaline phosphatase and cholinesterase activity in the small intestinal tissues, 4.4-fold increased endotoxin levels, 4.6-fold increased urea levels, twofold increased portal blood plasma creatinine levels, and twofold increased urinary indican excretion were observed three days after intravenous administration of CP in a dose of 390 mg/kg. Intragastric administration of $NaHCO_3$ or HCl partially prevented gastric stasis, but not acute gut-derived endotoxemia. Administration of $NaHCO_3$, not HCl, prevented enterocytopenia in the duodenum. Acute gut-derived endotoxemia resulted mainly from the more intense release of the cecal microflora waste products into blood. Testing the use of sodium bicarbonate intragastric administration combined with the enteral detoxification and/or options for suppression of colonic microflora vegetation for prevention of the myeloablative cytostatic therapy complications is promising.

**Keywords:** gastric stasis, sodium bicarbonate, myeloablation, hydrochloric acid, cyclophosphamide, endotoxemia, enterocytopenia

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**Compliance with ethical standards:** the study was compliant with the principles of bioethics adopted by the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes.

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# ВЛИЯНИЕ ВНУТРИЖЕЛУДОЧНОГО ВВЕДЕНИЯ ГИДРОКАРБОНАТА НАТРИЯ ИЛИ СОЛЯНОЙ КИСЛОТЫ НА КИШЕЧНУЮ ЭНДОТОКСЕМИЮ У КРЫС ПРИ МИЕЛОАБЛЯЦИИ ЦИКЛОФОСФАМИДОМ

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К токсическим эффектам циклофосфамида (ЦФ) в миелоабляционных дозах относится повреждение желудочно-кишечного тракта. Оно проявляется желудочно-кишечным стазом, цитостатическим повреждением слизистой оболочки тонкой кишки и острой кишечной эндотоксемией. Целью работы было выявить причинно-следственные связи между желудочно-кишечным стазом, энтероцитопенией и острой кишечной эндотоксемией при моделировании на крысах миелоабляционной терапии ЦФ. Изучали влияние вводимого в желудок 0,48 М раствора гидрокарбоната натрия ($NaHCO_3$) или 0,1 М раствора соляной кислоты (HCl) на показатели желудочно-кишечного стаза, энтероцитопении, содержание в портальной крови эндотоксина, аммиака, мочевины и экскрецию индикана с мочой. Через трое суток после внутривенного введения ЦФ в дозе 390 мг/кг наблюдали переполнение химусом желудка, снижение активности щелочной фосфатазы и холинэстеразы в тканях тонкой кишки, повышение содержания эндотоксина в 4,0 раза и мочевины в 4,6 раза при двукратном повышении уровня креатинина в плазме портальной крови, двукратное повышение экскреции индикана с мочой. Введение в желудок $NaHCO_3$ или HCl частично предупреждало гастростаз, но не острую кишечную эндотоксемию. Введение $NaHCO_3$, но не HCl, предупреждало энтероцитопению в двенадцатиперстной кишке. Острая кишечная эндотоксемия была обусловлена преимущественно интенсификацией поступления в кровь продуктов жизнедеятельности микрофлоры слепой кишки. Перспективна апробация внутрижелудочного введения гидрокарбоната натрия в сочетании с энтеральной детоксикацией и (или) применением средств подавления вегетации толстокишечной микрофлоры для профилактики желудочно-кишечных осложнений миелоабляционной цитостатической терапии.

**Ключевые слова:** гастростаз, гидрокарбонат натрия, миелоабляция, соляная кислота, циклофосфамид, эндотоксемия, энтероцитопения

**Вклад авторов:** О. А. Вакуненкова — экспериментальная часть работы; Е. А. Золотоверхая — биохимические исследования крови; Т. Б. Печурина — биохимические исследования тканей; Т. В. Шефер — экспериментальная часть, обработка и визуализация данных, разработка экспериментальной модели; Ю. Ю. Ивницкий — научный замысел, разработка экспериментальной модели, интерпретация и обсуждение результатов. Все авторы участвовали в обсуждении результатов, подготовке и редактировании рукописи статьи.

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In supralethal doses, cyclophosphamide (CP) is used for myeloablation with the aim of preparing recipients to hematopoietic stem cell transplantation. Side effects of such treatment include inhibition of gastrointestinal motility, cytostatic damage to the small intestine's epithelium, and endotoxemia. These complications disrupt enteral nutrition, reduce the effectiveness of orally administered drugs, and increase the likelihood of death of patients before transplantation. Gastrostasis and acute small intestinal mucositis, prevented by introduction of sodium bicarbonate solution (NaHCO3) into the stomach, were observed in rats after administration of a myeloablation dose of CP [1]. The currently unclear matters are the nature of the relationship between gastrointestinal stasis, enterocytopenia, and endotoxemia, and how $NaHCO_3$ or hydrochloric acid (agents that change the pH of gastric chyme) affect them. This study aimed to identify the relationship between gastrointestinal stasis, damage to the mucous membrane of the small intestine, and acute intestinal endotoxemia in the context of modeling myeloablation cytostatic therapy in rats.

## METHODS

We used male albino Wistar rats weighing 161–190 g (branch of the Kurchatov Institute – PNPI – Rappolovo Laboratory Animal Nursery; Russia). The animals received standard rat feed and drinking water *ad libitum*. We randomized the animals into four groups: 1) intact animals; 2) those who received CP only; 3) those who received CP and NaHCO3; 4) rats that received CP and HCl. Twenty-four hours after administration of CP, rats were placed in cages with a lattice floor that prevented coprophagia and eating of litter, with access only to water. Myeloablation was triggered by a single injection (into the tail's lateral vein) of a freshly prepared aqueous solution of Endoxan, a CP drug (Baxter Oncology GMBH; Germany). The dose was 390 mg /kg (≈ 1.7 $LD_{99/30\ days}$), the volume — 10 ml/kg. This dose of CP was 1.7 $LD_{99/30\ days}$, which allowed the rats to survive for at least 3 days after administration. Twice, 30 minutes before and immediately after administration of CP, the animals received intragastric injections of 0.48 M $NaHCO_3$ solution (pH = 8.34) in a volume of 15 ml/kg, or 0.1 M HCl solution (pH = 1) in the same volume. The animals were examined 72 hours after administration of CP.

The rats were put under halothane anesthesia for blood sampling from *v. portae* and organ extraction. To gage the gastrointestinal tract's (GIT) propulsive function, we measured the relative mass of gastric and intestinal chyme, which was calculated as the difference (in grams) between the mass of a chyme-filled and an empty organ (*gaster*, *caecum*), related to body weight (in kilograms). In parallel, we measured the relative mass of the spleen in order to assess the selectivity of action of $NaHCO_3$ or HCl.

To assess the severity of enterocytopenia in the small intestine's tissues, we assessed the activity of enterocyte markers: alkaline phosphatase, alkaline phosphatase (AP) [2], and cholinesterase (CE) [3]. Cranial segments of duodenum, caudal segments of jejunum and ilum (length — 4 cm each) were homogenized in a 15-fold volume of tris-HCl buffer (50 mM, pH = 7.4) and frozen at –20 °C. After 15 hours, the homogenates were thawed at 4 °C and centrifuged at 2000 g for 10 minutes. In the supernatant, we established the activity of AP with the help of the kinetic optimized method and using a set of reagents (Olvex Diagnosticum; Russia), and assessed the activity of CE using Ellman's assay, substrate of acetylthiocholine iodide (Sigma-Aldrich; USA), and ChemWell 2910 biochemical analyzer (Awareness Tech.; USA). Another determined parameter was protein content, which we quantified using the Bradford method.

The assessment of intestinal endotoxemia was based on the content of endotoxin and ammonia in portal blood plasma, and urea, which is the product of neutralization of ammonia by the liver. Endotoxin was detected with a LAL reagent in the gel-thrombus test modification, the process enabled by the ALPYR Test reagent kit (Algimed Techno LLC; Russia). To increase sensitivity, we incubated the samples at 70 °C for 15 minutes before diluting them and mixing with the LAL reagent, thus unbinding the endotoxin from albumin [4]. Ammonia concentration was determined spectrophotometrically using the Ammonium Ultra reagent kit (Sentinel Diagnostics; Italy). Concentration of urea was established after its hydrolysis to ammonia, with the help of the Urea UV reagent kit (Biosystems; Spain). Concurrently, we measured blood plasma concentrations of creatinine (reaction with picric acid), albumin (reaction with bromocresol green), and total protein (reaction with acid blue 90).

Urinary excretion of indican was used as an indicator of excessive bacterial growth [5]; for this purpose, we collected urine while the animals were in metabolic chambers from 48$^{th}$ to 72$^{nd}$ hour after administration of CP. Indican was quantified with Obermayer reagent [6], and excretion was expressed in micrograms per kilogram of body weight per hour.

The results were given as a mean and an error of mean ($M \pm m$). We applied ANOVA to assess the effect of the administered substances on the studied quantitative indicators. When the models reached significance, the means between groups were compared through Tukey's honest significant difference test [7]. The differences were considered significant at $p = 0.05$.

## RESULTS

After two days of fasting, chyme was concentrated only in gaster and caecum. Animals that received CP had the relative mass of gastric chyme 10.5 times greater than intact animals, while the mass index of the caecal chyme did not differ significantly between the groups. Both $NaHCO_3$ and HCl partially prevented the overfilling of stomach with chyme, but did not change the volume of content of caecum (Fig. 1).

Administration of CP led to enterocytopenia. The activity of AP decreased 1.6–4.9 times in all parts of the small intestine, most significantly in the ileum; the activity of ACE was reduced only in the ileum. $NaHCO_3$ partially prevented the decrease of activity of AP in duodenum (Fig. 2). Neither $NaHCO_3$ nor HCl influenced the systemic cytopenic effect of CP, which made the spleen's relative weight 57% smaller (Fig. 1).

In intact rats, the portal blood plasma ammonia content was 0.88 mM, three times higher in plasma after decapitation [8]. Administration of CP did not change the blood ammonia level significantly, but content of urea has grown 4.6 times. $NaHCO_3$, administered by gavage, made the level of urea increase further, and HCl halved it, but the said level still remained higher than in the control group. After administration of CP, the portal blood endotoxin content was 4 times higher than in intact animals, with $NaHCO_3$ or HCl having little effect on this parameter. The concentration of creatinine in blood of rats that received CP was twice as high as in intact animals, and remained largely the same after administration of $NaHCO_3$ or HCl. There were no significant intergroup differences in the content of total protein or albumin in blood plasma (Figure 3). Administration of CP intensified urinary excretion of indican two-fold, with HCl unable to change the respective dynamics.

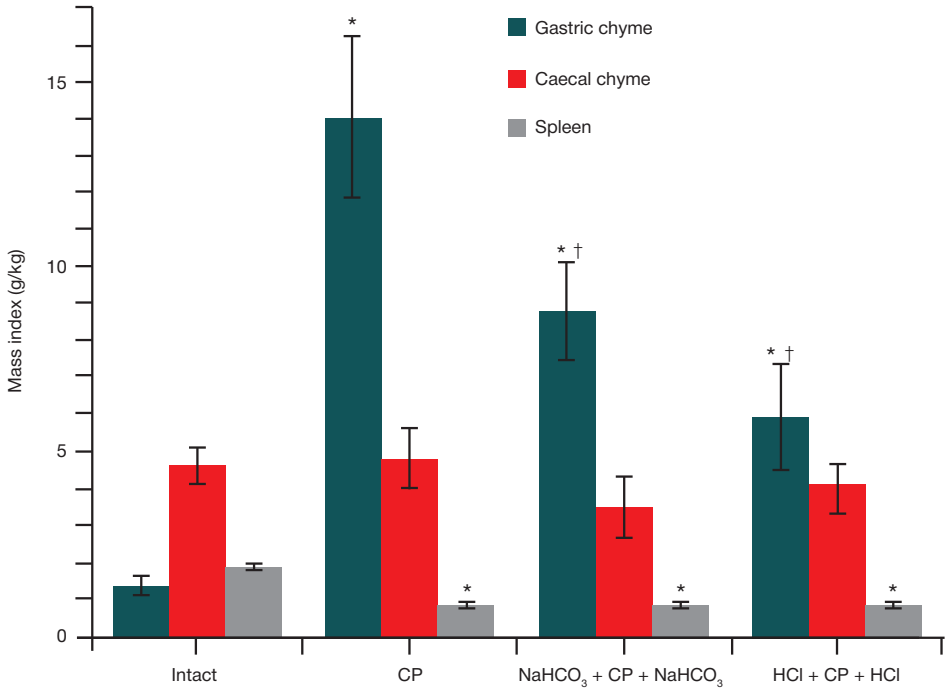


**Fig. 1.** Mass indexes of gastric, caecal chyme, and spleen in rats 72 hours after intravenous administration of cyclophosphamide (M ± *m*; *n* = 8). Intact — rats that received no medicines; CP — rats that received only cyclophosphamide; $NaHCO_3$ + CP + $NaHCO_3$ — intragastric administration of 0.48 M of sodium bicarbonate 30 minutes before and immediately after cyclophosphamide; HCl + CP + HCl — intragastric administration of 0.1 M of hydrochloric acid 30 minutes before and immediately after cyclophosphamide. Significant difference, $p < 0.05$: * — with intact group; † — with the CP group

Intragastric injection of $NaHCO_3$ induced hyperindicanuria as a trend (Fig. 4).

## DISCUSSION

After the animals are deprived of food, the mass of their gastric contents is determined by the propulsive function of the stomach. Therefore, the overfilling of stomach with chyme after administration of CP, which we registered in this and the previous study [1], reflected the development of gastrostasis. If the change in gastrointestinal motility were limited to gastrostasis, then the flow of chyme into the cecum would have happened after its emptying, and the relative mass of chyme therein would have been decreasing. However, against the background of administration of CP, the mass of the caecal chyme did not change significantly (Fig. 1). This means that CP inhibited the propulsive function not only in the stomach, but also in the colon.

It can be assumed that gastrostasis was a protective response aimed at preventing chyme from injuring the small intestine, the part of the gastrointestinal tract most sensitive to CP. The damage thereto manifested as enterocytopenia, as indicated by the decreasing content of enterocyte markers in the small intestine's tissues (Fig. 2). Another consequence of gastrostasis could be restricted delivery of substrates to bacteria vegetating in the lumen of the colon. In its chyme, the specific content of bacteria is eight orders of magnitude higher than in the chyme of the stomach [9], which makes colonic microflora the source of endotoxemia. Given the division frequency of 3 $h^{-1}$ (the mean for *Escherichia coli* at 37 °C), it is theoretically possible that the amount of bacteria increases eightfold within an hour after colon loses the propulsive function. Substrate limitations stemming from gastrostasis could restrain such a rapid growth of colonic microflora, as well as production of ammonia thereby. However, gastrointestinal

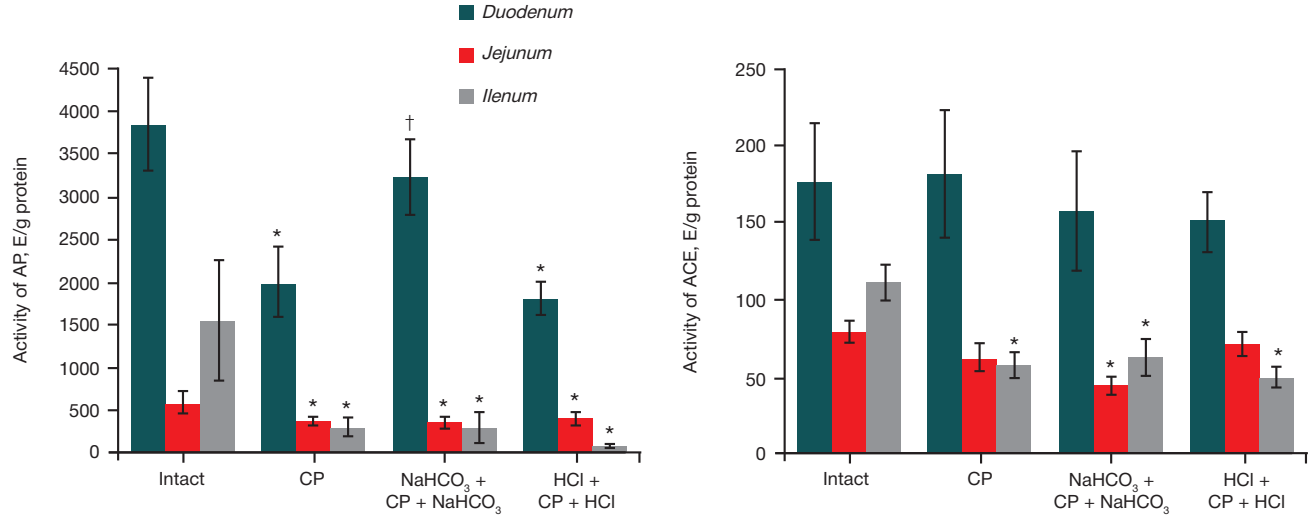


**Fig. 2.** Activity of alkaline phosphatase (left) and cholinesterase (right) in rats' small intestine tissues 72 hours after administration of cyclophosphamide (M ± *m*; *n* = 8). Significant difference, $p < 0.05$: * — with intact group; † — with the CP group

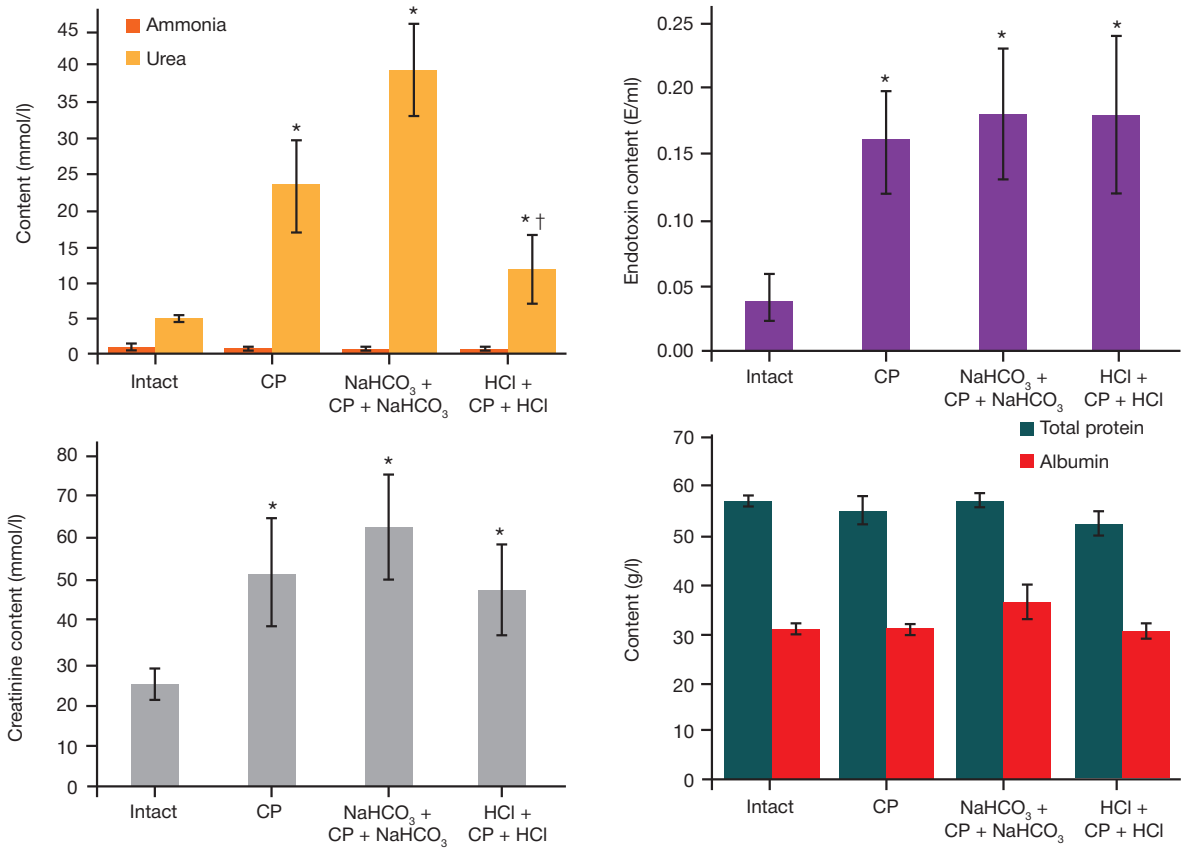


**Fig. 3.** Content of ammonia, urea, endotoxin, creatinine, albumin, and total protein in blood plasma sampled from rats' portal veins 72 hours after administration of cyclophosphamide (M ± *m*; *n* = 8). Significant difference, $p < 0.05$: * — with intact group; † — with the CP group

stasis could not suppress ammonia-producing wall microflora, the substrates for which are substances diffusing to the luminal surface of the gastrointestinal mucosa from the blood. Colon stasis, which prevented discharge of the ammonia-producing microflora from the body, could have promoted production of ammonia in the caecum. Ammonia produced by the intestinal microflora becomes part of urea in the liver. Its content in the blood of animals that received CP increased fourfold three days after administration (Fig. 3), which means that production of ammonia in the intestine was intensified earlier. This hypothesis is supported by an almost twofold spike of the level of blood ammonia 3 hours after administration of myeloablation dose of CP [8]. Partially, uremia could also have been associated with a delay in the excretion of urea from the body, as backed by a twofold increase of the blood level of creatinine, a marker of renal insufficiency. Therefore, the increase in blood urea levels registered in this study 3 days after administration of CP was a marker of acute intestinal endotoxemia of a mixed type, productive and retention.

In the animals that received CP, gram-negative bacteria, which are the source of endotoxin, could be concentrated in the stomach and caecum, since other parts of the gastrointestinal tract were free of chyme. The content of endotoxin in the colonic chyme is close to 2.5 g/l [10], and its release from bacteria could have been intensified by their death due to substrate limitations imposed by gastrostasis. Colonic stasis increased the duration of endotoxin contact with the sorbing surface of the mucous membrane, therefore portal endotoxinemia after administration of CP (Fig. 3) could have been both productive and redistributive. The lack of effect of CP on the blood plasma protein level indicates that the content of endotoxin in biologically active free form increased in proportion to its total plasma content.

Indican is the end product of metabolism of indole, the only source of which in the experimental conditions was a reaction catalyzed by tryptophanase of the intestinal microflora. Hyperindicanuria is a valid indicator of excessive growth of indole-producing bacteria in the gastrointestinal tract [5]. Urinary excretion of indican intensified (Fig. 4) despite the impairments of the renal excretory function, which were confirmed by the increased blood level of creatinine (Figure 3). In the CP group, this indicates the predominance of productive and (or) redistributive component of intestinal endotoxemia over the retention component.

Both $NaHCO_3$ and HCl partially prevented gastric overfilling in rats (Fig. 1), and only $NaHCO_3$ could stop enterocytopenia to a certain degree. The alkalizing effect of $NaHCO_3$ was predominantly local, since it prevented enterocytopenia only in the duodenum, but not in the caudal parts of the small intestine and not in the spleen (Fig. 2). This supports the hypothesis [1] that has lower cytostatic damage to the mucous membrane's epithelium a probable mechanism of prevention of gastrostasis (induced by CP) by $NaHCO_3$. Administration of HCl partially prevented gastric overfilling, which could have been the result of the boost it gave to pepsin [11], and accelerated digestion of feed consumed by the animals in the next 24 hours. This explanation is supported by data on the depressing effect of CP on gastric secretion [12].

The severity of intestinal endotoxemia depends on the intensity of release of toxicants by the intestinal microflora, permeability of the enterohematic barrier, and the rate of their excretion from the body. Rats that received CP had the cytostatic damage most pronounced in the small intestine [13], while the intestinal microflora was concentrated in the stomach and caecum, where mucosal epithelium is more resistant to cytostatics. Therefore, cytostatic damage to the small intestine

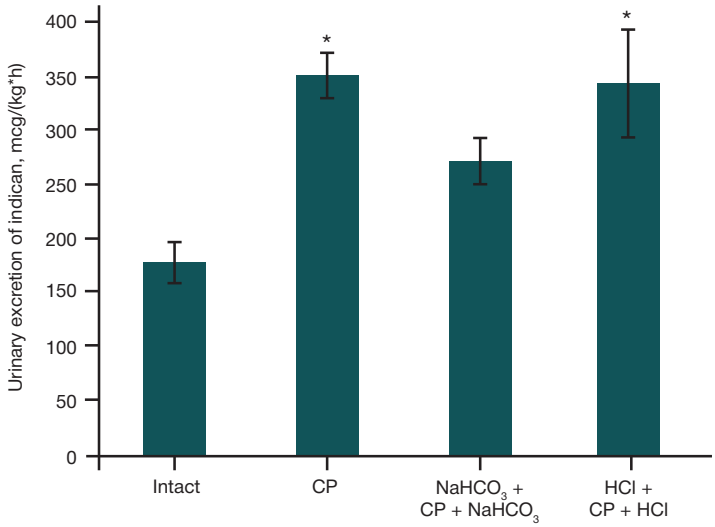


**Fig. 4.** Urinary excretion of indican, 48th to 72nd hours after administration of cyclophosphamide (M ± *m*; *n* = 8). * — significant difference with the intact group, $p < 0.05$

could not directly affect the appearance of intestinal toxicants in blood. This is further evidenced by the lack of a significant effect of $NaHCO_3$, which reduced the severity of enterocytopenia, on the portal blood level of endotoxin (Fig. 3) and severity of indicanuria (Fig. 4) in rats that received CP. The difference in the effect of $NaHCO_3$ and HCl on the portal blood level urea, product of neutralization of ammonia (Fig. 2), could have been conditioned by ammonia becoming $NH_3$ in the alkaline medium, a free form that easily diffuses through biomembranes [14], while in the acidic medium ammonia was in its ionized form $NH4^+$, which can hardly penetrate enterohematic barrier.

Thus, in a rat model of myeloablative cytostatic therapy, prevention of gastrostasis or cytostatic damage to the small intestine — complications of the said therapy — does not suppress acute intestinal endotoxemia. It is feasible to consider intragastric administration of $NaHCO_3$ in combination with agents suppressing vegetation of the colonic microflora when developing measures to prevent complications of myeloablation cytostatic therapy. These measures can be supplemented by enteric detoxification (enterosorption, intestinal lavage) aimed at removing endogenous toxicants from the sites of their secretion [15].

## CONCLUSIONS

Intravenous administration of a myeloablation dose of cyclophosphamide to rats causes gastrointestinal stasis, cytostatic damage to the mucous membrane of the small intestine, and development of a mixed-type acute gut-derived endotoxemia. The latter, in a rat model of myeloablative cytostatic therapy, was predominantly caused by penetration into blood of waste products of the caecum microflora. Intragastric administration of weak solutions of sodium bicarbonate or hydrochloric acid helps prevent gastrostasis triggered in rats by the myeloablative effect of cyclophosphamide, but these solutions do not stop acute intestinal endotoxemia. Intragastric administration of weak solutions of sodium bicarbonate prevents enterocytopenia triggered in rats by the myeloablative effect of cyclophosphamide, but it cannot halt the development of acute intestinal endotoxemia. For the measures designed to counter gastrointestinal toxicity of cyclophosphamide in the context of myeloablative cytostatic therapy, it is feasible to consider administration of sodium bicarbonate in combination with agents for enteric detoxification and suppression of vegetation of the colonic microflora.

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