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## The effect of the reparative action drug in treatment of pediatric duodenal ulcer

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**Background.** Digestive tract diseases occupy one of the first places in the structure of childhood pathology, including duodenal ulcers (DU), the development of which in 70–100% of cases is associated with *H.pylori* infection. It is found that the important role in the development of inflammatory process in digestive tract have toll-like receptors 4 (TLR4), due to reactivity to *H.pylori*. It is proved that growth factors, in particular epidermal growth factor (EGF), are able to influence on the healing processes in the mucous membrane. It is advisable to include drugs of reparative action in complex treatment of pediatric DU.

**Purpose** — to evaluate the effect of the reparative action drug in the treatment of pediatric DU, taking into account the dynamics of TLR4 and EGF in blood serum.

**Materials and methods.** The total clinical group consisted of 39 children aged 7–18 years with *H.pylori*-associated duodenal ulcer. In 20 patients of the group 1 with DU a standard triple regimen was used. In 19 patients of the group 2 a drug of reparative action was included. The content of TLR4 and EGF in serum were determined by ELISA.

**Results.** It was found that the level of TLR4 decreased by 15.1% and 27.5% after a course of treatment in patients of the group 1 and in the group 2, respectively compared to a level before treatment. It is showed that in patients of the group 1 and the group 2 after 3 weeks from the start of treatment there were changes in the content of EGF manifested by a decrease by 19.81% and 23.3%, compared to a level before treatment.

**Conclusions.** Our results indicated that after the course of treatment the content of TLR4 and EGF in the group 1 of patients was lower by 12.37% and 3.49% respectively, than in the group 2.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

**Keywords:** children, duodenal ulcer, *H.pylori*, drug of reparative function.

### Ефект препарату репаративної дії в терапії виразки дванадцятипалої кишки у дітей

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**Актуальність.** Захворювання травного тракту посідають одне з перших місць у структурі патології дитячого віку, і за останні десятиліття відзначається зростання їх поширеності до 75%, у тому числі виразки дванадцятипалої кишки (ВДПК), розвиток та хронічний перебіг якої у 70–100% випадків пов'язаний з інфекцією *H.pylori*. Відомо, що важливу роль у розвитку запального процесу в слизовій оболонці травного тракту відіграють тол-подібні рецептори 4 (TLR4), оскільки ці рецептори володіють реактивністю до *H.pylori*. Також доведено, що ростові фактори, зокрема епідермальний фактор росту (EGF), здатні впливати на процеси загоєння в слизовій оболонці. У лікуванні ВДПК рекомендовано застосовувати лікарські засоби репаративної дії. Перспективним у цьому напрямку є використання засобів рослинного походження.

**Мета** — оцінити ефект застосування препарату репаративної дії в терапії ВДПК у дітей з урахуванням динаміки TLR4 та EGF у сироватці крові.

**Матеріали та методи.** Загальну клінічну групу становили 39 дітей віком 7–18 років, хворих на *H.pylori*-асоційовану ВДПК. У 20 пацієнтів із ВДПК, асоційованою з інфекцією *H.pylori*, що становили групу 1, застосовували потрійну схему протягом 7 діб. У 19 хворих групи 2 до лікування додавали лікарський засіб репаративної дії. Вміст TLR4 та EGF у сироватці крові визначали методом ELISA.

Результати. Встановлено, що в пацієнтів групи 1 та групи 2 через 3 тижні від початку лікування спостерігали значні зміни вмісту EGF порівняно з рівнем у сироватці крові до початку лікування, проявляючись зниженням на 19,81% і 23,3% відповідно ( $p < 0,05$ ). Виявлено, що рівень TR4 зменшився на 15,1% та 27,5% після курсу проведеного лікування як у пацієнтів групи 1, так і групи 2 відповідно порівняно з рівнем до початку лікування.

**Висновки.** У дослідженні виявлено, що після курсу лікування препаратом, що володіє репаративною дією, вміст TLR4 та EGF у групі 1 був меншим на 12,37% і 3,49% відповідно, ніж у дітей, хворих на ВДПК, із групи 2.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду батьків, дітей.

Автори заявляють про відсутність конфлікту інтересів.

**Ключові слова:** діти, виразка дванадцятипалої кишки, *H.pylori*, препарат репаративної дії.

### Introduction

Digestive tract diseases occupy one of the first places in the structure of childhood pathology and in recent decades there has been an increase in their prevalence to 79.3% [9], including duodenal ulcer (DU), which is a common multifactorial disease, the development and chro-

nic course of which in 70–100% of cases is associated with an infectious process in the mucous membrane initiated by *H.pylori* [1]. It is known that *H.pylori* leads to the formation of chronic gastritis, the nature of which determines the full range of conditions associated with infection — from asymptomatic course to the development of gastric

cancer [8]. An important role in the development of *H.pylori*-associated DU is played by toll-like receptors 4 (TLR4), which are reactive to lipopolysaccharides of gram-negative bacteria [6]. Thus, due to the ability to express TLR4, epithelial cells can detect typical pathogen-associated molecular patterns (PAMP) of microbial or other origin. Recognition of PAMP by TLR4 activates the cascade of intracellular responses, which can manifest in the form of increased secretion of cytokines, peptide mediators, defensins, inhibitors of pro-inflammatory agents.

Considerable attention is paid to determining the effect of *H.pylori* on the processes of the duodenal mucosa regeneration, which is carried out using a number of substances of endogenous origin, such as epidermal growth factor (EGF), which accelerates migration and proliferation of epithelium. Scientists have established that EGF in combination with other cytokines is the most important factor that indirectly affects on the healing process [7].

It is important and relevant to improve the prognosis of peptic ulcer and search for drugs that have a complex and positive effect on treatment results by accelerating regenerative processes and the impact on the inflammatory process, while meeting the safety requirements in pediatric practice. Promising in this direction is the use of herbal drugs [5]. The basis of the drug of reparative action are liquid extracts of seven medicinal plants, widely used in gastroenterology. Thus, the substance of wormwood improves gastric motility. In particular, licorice root contains glycyrrhizinic acid, which has a powerful anti-inflammatory effect and stimulates the formation of granulation tissue, as well as provides an antispasmodic effect. Chamomile, in addition to anti-inflammatory effect, contains components that have anti-allergic and regenerating effects, thistle fruits have a cytoprotective effect.

The components of this drug reduce the severity of the inflammatory process and accelerate its reparative stage. The drug of reparative action improves abdominal blood circulation and accelerates the healing of ulcers, by stimulating the formation of granulations at the site of the ulcer defect of the mucous membrane and increase its vascularization, reduces the severity of symptoms and has a positive effect on the autonomic nervous system.

Due to the multifaceted positive effect on the body, the ability to maximize its manifestation in the area of the pathological focus, the drug

can have a positive effect on the inflammatory process in duodenal mucosa, and make faster and more complete recovery of the mucous membrane.

**Purpose** of the study – to evaluate the effect of the reparative action drug in the treatment of pediatric DU, taking into account the dynamics of TLR4 and EGF in blood serum.

### Materials and methods

The total clinical group consisted of 39 children aged 7–18 years with *H.pylori*-associated DU. Under observation there were 24 (61.54%) boys, representing of the total number of examined patients with DU, and 15 (38.46%) girls. In 20 patients of the group 1 with *H.pylori*-associated DU a standard triple regimen was used for 7 days. In case of increased acid-forming function of the stomach, H<sub>2</sub>-histamine blockers (1–2 mg/kg/day) were added to children before 12 years old, and proton pump inhibitors (0.5–0.8 mg/kg/day) were added after 12 years. At the same time with the use of these drugs before treatment in 19 patients of the group 2 a drug of reparative action was included in the dosage recommended for use in pediatric practice (children over 12 years – 20–30 drops, in children aged 6 years old 1 drop per year of life 3 times a day *per os* for 3–4 weeks of treatment).

The control group consisted of 25 healthy children of the appropriate age. The mean age of patients was 13.3±0.2 years old. Clinical, laboratory and instrumental methods of examination were used in the study. All children underwent esophagoduodenoscopy using the video system «VIDEO SYSTEM OTV-SC, OLIMPUS GIF-XPE». An urease test (URE-HPtest) was used to diagnose *H.pylori* infection. The content of TLR4 in the blood serum was determined by enzyme-linked immunosorbent assay according to the set «Human TLR4 ELISA Kit» (NeoBiolab, USA) according to the manufacturer's instructions. Serum epidermal growth factor (EGF) was determined by enzyme-linked immunosorbent assay (ELISA) using the Human EGF ELISA Kit (Invitrogen, USA). Statistical processing of the obtained data was carried out according to the generally accepted methods of variation statistics. Basic statistical indicators were determined – arithmetic mean (M), mean error (m), p – achieved level of statistical significance, n – volume of the analyzed group. The probability of differences in the compared groups was assessed by standard parametric and nonparametric methods using Student's criteria. The effectiveness of therapy was performed

**The content of EGF in the serum of children with duodenal ulcer, Me (25–75)**

Table 1

Group of patients	EGF, pg/ml		
	(M±m)	Me	25–75-percentile
Group 1, n=20	641.01±42.58*	642	515–726.5
Group 2, n=19	625.8±33.17	626	483–727
Control group, n=25	284±22.67	280	206–332

Note: \*p<0,05 — the difference is probable with respect to the group of healthy children.

**The content of TLR4 in the serum of children with peptic ulcer, Me (25–75)**

Table 2

Group of patients	TLR 4, pg/ml		
	M±m	Me	25–75-percentile
Group 1, n=20	1713.50±190.95*	1560	1230–2085
Group 2, n=19	1667.9±143.6	1420	1230–2010
Control group, n=25	672±36.43	658	528–768

Note: \*p<0.05 — the difference is probable with respect to the group of healthy children.

three weeks after the start of treatment. It was calculated Mediana (Me), (25–75)-percentile.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.

### Results and discussion

We studied the biochemical marker of proliferation EGF, as well as the level of TLR4 in the serum of patients in both groups. Prior to therapy, both observation groups did not differ significantly in age, sex, course of the disease, laboratory parameters and morphofunctional changes in the organs of the gastroduodenal system. Before starting therapy, there were no differences between patients in the compared groups and the severity of clinical manifestations of DU.

In children with DU, the features of the mechanisms that regulate reparative processes under the influence of standard treatment and with the inclusion of the reparative action drug were determined, for which the dynamics of EGF in serum was assessed. Significant differences in serum EGF levels in patients of the group 1 and the group 2 before treatment were absent.

All patients with DU, who were monitored before treatment had significantly higher serum EGF values compared to healthy children (Table 1). Thus,

there was an increase in EGF 55.69% and 54.62% to 641.01±42.58 pg/ml (p<0.05) in the group 1 and to 625.8±33,17 pg/ml (p<0,05) – in the group 2.

It was found that in patients of the group 1 and the group 2 after 3 weeks the of treatment there were significant changes in the content of EGF compared with the level in the serum before treatment, manifested by a decrease to 514.51±32.96 pg/ml (p<0.05) and 479.4±32.59 pg/ml in 19.81% and 23.3%, respectively, and approximation to the values of healthy children. Our results indicated that after the course of treatment, the EGF content in patients of the group 2 was lower 3.49% respectively, than in children with duodenal ulcer the group 1.

It has been observed that in all children with duodenal ulcer before the therapy was significantly increased content of TLR4, compared with healthy children: up to 1713.50±190.95 pg/ml in the group 1 and up to 1667.9±143.6 pg/ml (p<0.01) in the group 2 by 59.71% and 60.78% (Table 2).

It was found that the level of TLR4 decreased to 1453.0±165.7 pg/ml and 1208.4±111.24 pg/ml by 15.1% and 27.5% after a course of treatment in both patients of the group 1 and in the group 2 (p<0.05), respectively.

After treatment, the content of TLR4 in patients of the group 2 was lower by 12.37%, than in children with duodenal ulcer the group 1 (Table 3).

Similar features of TLR4 changes in blood serum at this stage of supervision are caused by more expressed decrease in inflammatory changes

**The dynamics of the content EGF, TLR4 in the serum of children with duodenal ulcer before and after treatment**

Table 3

Group of patients	TLR4, pg/ml		EGF, pg/ml	
	before treatment	after treatment	before treatment	after treatment
Group 1, n=20	1713.50±190.95	1453.0±165.7	641.01±42.58	514.51±32.96
Group 2, n=19	1667.9±143.6	1208.4±111.4*	625.8±33.17	479.4±32.59*

Note: \*p<0.05 — the difference is probable.

## ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

of a mucous membrane at patients who received drug of reparative action.

### Conclusions

The research suggests the need for inclusion drugs of reparative action in complex treatment of duodenal ulcer that can positively effect on the pathogenesis link of the disease.

Evaluation of the main clinical symptoms of the disease showed that in all patients the therapy gave positive results in the form of improvement of general condition, significant reduction or disappearance of pain, dyspeptic syndrome. However, it should be noted that against the background of complex therapy with a drug of reparative action in all patients there was a complete elimination of the disease, and when using only the eradication scheme in 1 (5%) of 20 patients remained episodic abdominal pain and heartburn.

Serum analysis showed that in patients of the group 1 and the group 2 after 3 weeks from the

start of treatment there were significant changes in the content of EGF manifested by a decrease 19.81% and 23.3%, respectively.

It has been observed that, TLR4 were significantly increased in all children before therapy, compared with healthy children in the group 1 by 59.71% and by 60.78% in the group 2 ( $p < 0.01$ ), respectively. It was found that the level of TLR4 decreased by (15.1% and 27.5%) after a course of treatment in patients of the group 1 and in the group 2 ( $p < 0.01$ ), respectively.

Against the background of taking the drug, which has a reparative effect, there was a decrease in the content of TLR4 and EGF at the level that could help improve the recovery processes in duodenal mucosa.

Thus, after 3 weeks of treatment with drug of reparative function, the content of TLR4 and EGF in the group 1 of patients was lower by 12.37% and 3.49%, respectively, than in the group 2.

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