MEDICATIONS FOR ERADICATION OF HELICOBACTER PYLORI (REVIEW)

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Helicobacter pylori (H. pylori) is a pathogenic bacteria that affects more than 4 billion people in the world causes chronic gastritis, and may lead to severe complications, such as peptic ulcer disease, gastric MALT lymphoma, and gastric cancer. The strong link between Helicobacter pylori and the development of stomach cancer has been shown by new research. Infection with H. pylori produces inflammation of the stomach mucosa, a reduction in the protective alkaline layer, and changes in gastric acidity. The release of hydrochloric acid rises when an infection induced by H. pylori penetrates the upper section of the stomach. The chance of getting a duodenal ulcer increases along with the acidity of the stomach contents. Chronic atrophic gastritis impairs the functioning of parietal cells, which release hydrochloric acid, increasing the risk of stomach ulcers and cancer[1,2,3].

Nonsteroidal anti-inflammatory medicines (NSAIDs), such as acetylsalicylic acid, suppress prostaglandin synthesis and hence diminish the creation of a protective alkaline layer, increasing the risk of stomach ulcer[9].

Helicobacter pylori is widespread and occurs in 50-80% of Asians, 70-90%of Africans, 30% of United States, 70% of Eastern Europeans, 30-50%of Western Europeans, and 20% of Australians. The spread of H. pylori infection is influenced by age, ethnicity, gender, geography and socioeconomic status[4,5].In the population of less developed countries, Helicobacter pylori is more common. H. pylori can be spread by water, plants, animal feeds, and other sources[2,5].

One out of every ten H. pylori patients gets a stomach ulcer, and one out of every 100 patients develops gastric cancer. The substancesgenerated by H. pylori are extremely similar to those produced by the stomach of the host. Since its discovery, several trials have been carried out to effectively eradicate H. pylori, both in vitro and in vivo. Proton pump inhibitors, antibiotics of various classes, bismuth salts, and other substances were examined. Recently researches revealed that traditional treatment regimens for H. pylori eradication are often ineffective, with failure rates as high as 30-40% [3-7,9,10,12].

The growing resistance of H. pylori to clarithromycin, an important component of the traditional triple eradication regimen, is one of the key reasons limiting successful therapy [9,15,16]. Other factors contribute to the ineffective eradication of H. pylori are as follows:

- Increased resistance of H. pylori to antibiotics in general[9,10];
- Cytotoxicity of the intestinal flora and overall toxicity of proton pump inhibitors and antibacterial medicines [9,10];
- Patients negative attitudes toward treatment and the prescription's vulnerability [17-19];
- Antibiotic bioavailability during oral administration is inhibited by the gastric mucosa [2].

In light of rising resistance to H. pylori medicines, it's critical to improve current H. pylori eradication strategies and incorporate additional medicines into the treatment process [20-22]. Development of an antibiotic-free alternative treatment regimen is based on research study[2,23]:

- Addition of De-Nola (BISMUTHATE, TRIPOTASSIUM DICITRATO) in the pharmacotherapeutic regimen [24,25];
- Use of high doses of second-generation proton pump inhibitors. They increase antibiotic resistance at low pH;
- Involvement of Azithromycin (macrolide) in the triple therapy regimen;
- Involvement of a 30% aqueous solution of propolis and vitamin C in complex pharmacotherapy for H. pylori eradication [26-29].

It's worth noting that antibiotic therapy is unsuccessful in 20% of patients, leaving 140 million individuals worldwide without analternative therapeutic option. In addition, due to the rise in antibiotic resistance, the cure rate decreases year after year.As no new broad-spectrum antibiotics have been identified to yet, additional focus should be made on alternative antimicrobial substances, such as: probiotics, prebiotics and bio-active compounds of plant origin [11-13,15,45].

The appropriateness of including probiotics in the pharmacotherapeutic scheme of H. pylori eradication is recognized by the Fourth Maastricht Consensus (2010). Bifidobacterium, lactobacillus, and some other microorganisms such as Saccharomyces boulardii are used as probiotics [8,15,30,34].

The mechanism of action of probiotics on the human body is revealed in three stages:

In the first stage - probiotic bacteria inhibit the viability of pathogenic strains by competing for nutrients [31-33].

At the second stage, probiotic bacteria inhibit the adhesion of pathogenic microflora and resist the translocation of the intestinal pathogenic microflora into the inner area of the macroorganism [31-33].

At the third stage, probiotic bacteria are involved in the activation of the local and general immune response [31-33].

It is noteworthy that probiotic preparations contain living cells of the microflora, predominantly bifidobacterium and lactobacillus. During oral administration, the majority of them are inactivated by gastric acid. As only 5-10% of live bacteria reach the large intestine and begin to coexist, prebiotics that are not digested and absorbed in the upper section of the intestine must be added, furthermore, they are selectively fermented by the microflora in the large intestine, which increases the life expectancy and coexistence of beneficial microflora [34].

Prebiotics, unlike probiotics, have a slower effect on the body, hence their usage is more long-term. They provide food for the beneficial intestinal microflora and create ideal conditions for their life and development [18,34].

Prebiotics are thermally stable. They improve the absorption of some minerals, significantly enhance immune factors on the walls of the large intestine, increase the body's resistance to infections, and improve intestinal peristalsis. The main prebiotics are - carbohydrates: breast milk lactulose, inulin, pectin, dietary fiber, topinambur flour and etc. [18,34].

Prebiotics are in their purest form in breast milk: milk sugar, lactose (90%) and oligosaccharide (10%). However, breast milk is predominantly beta-lactose, while cow's milk contains alpha-lactose. The latter does not have prebiotic properties. Accordingly, the bifidogenicity of breast milk is 40 times higher than thebifidogenicity of cow's milk [23,34].

Based on scientific studies, sufficient knowledge has been accumulated regarding the use of biologically active substances of plant origin (peptides, polyphenols, terpenes, fatty acids, etc.) for impact on Helicobacter pylori [2]. The acid fraction extracted from the woody gum of the evergreen plant Pistacia lentiscus (Pistacia lentiscus L., family Anacardiaceae, genus Pistacia L.), which has been demonstrated to possess bactericidal activity against 11 strains of H. pylori, is of particular interest in this regard [47,48].

Modern scientific studies have confirmed Pistacia lentiscus L.'s therapeutic benefits in gastrointestinal disorders, revealing it's in vivo and in vitro activity against Helicobacter pylori, which is considered to be the main cause of gastric ulcer. In addition, it has antimicrobial, fungicidal, antioxidant, hypolipidemic, anti-inflammatory, anti-tumor action and etc. [47,48].

In 2015, Pistacia lentiscus L. gum was recognized as an herbal medicinal product by the European Medicines Agency (EMA) with two therapeutic indications - mild dyspeptic disorders and skin inflammation / healing of minor wounds. In recent years, Chios mastic gum has been widely used in medicinal products, food supplements and cosmetics [47,48].

Experimental studies have shown that the alcoholic extract of the fruit of the apricot (Armeniaca vulgaris L.) has an inhibitory effect on the development of Helicobacter pylori, which is due to the content of syringa resinol [36,37]. Experimental studies have also shown that the roots of Acorus (Acorus calamus L.) have an inhibitory effect on urease activity [36-39].

Inhibitory effect of Anisum (Anisum vulgare Goerth.) extract on Helicobacter pylori has been shown in the literature. A similar effect was confirmed in an experiment with an alcoholic extract of orange (Citrus sinensis (L.) Osbeck.) peel [40]. Barberry extract (Berberis vulgaris L.) inhibits the processes caused by Helicobacter pylori, protects against the development of stomach ulcers and tumors [41]. Grape fruit (Vitis vinifera L.), due to its anti-inflammatory and antioxidant properties, acts on Helicobacter pylori and has an anti-ulcer effect [42,43]. It has been established that quercetin and resveratrol from grape fruit also affect H. pylori [44]. Experimental studies have shown that the peel of the pomegranate (Punica granatum L.) exhibits bactericidal activity against Helicobacter pylori. A similar effect is a characteristic fororangejuice (Citrus paradisi Macf.), Walnut leaf extract, artemisinin(from Artemisia annua L.), exhibits anti-ulcer action, savory (Satureja hortensis L.) and essential oils of oregano (Origanum tuttahantumGontsch), Coriander (Coriandrum sativum L.) extract protects the gastrointestinal tract from the negative effects of Helicobacter pylori [35].

Experimental studies have shown that cinnamon aldehyde (from Cinnamomum Blume L.) has a therapeutic effect on H. pylori-induced gastritis. The protein arabinogalactan isolated from the seeds of black currant (Ribes nigrum L.) inhibits the adhesion of Helicobacter pylori to the stomach walls. Licorice (Glycyrrhiza glabra L.) root flavonoids, 18-β-glyceretic acid has bactericidal action on H. pylori. Randomized, placebo-controlled studies have shown that GutGard (a flavonoid-rich extract of licorice roots) is an effective approach to eradicate H. pylori. Due to its enveloping properties, licorice roots preparations are an effective remedy for gastric ulcer. The inhibitory effect of fennel (Foeniculum vulgare Mill.) Extract on the development of H. pylori has been established. Experimental studies have shown that methanolic extract of black pepper (Piper nigrum L.) prevents Helicobacter pylori fromadhering to gastric adenocarcinoma cells. Garlic (Allium sativum L.), even in small doses kills Helicobacter pylori, this property can be used for prevention of both,stomach ulcers and tumors. Prescribed anti-ulcer action Rumex (Rumex confertusWilld.). Propolis extract inhibits the enzyme Helicobacter pylori deformylase and prevents the development of gastric ulcer [35,38,46]. The mechanism of anti-Helicobacter action of polyphenolic compounds is described in the literature [2].

To eradicate H. pylori, effective systems for modified drug delivery and release must be developed, which may be employed to accomplish the following tasks:

- ✓ Regulation of the rate and duration of release of the medicinal substance;
- ✓ Improving the therapeutic effect;
- ✓ Protection of the medical substance from the effects of gastric juice hydrochloric acid and digestive enzymes;
- ✓ Delay transit in the stomach;
- ✓ Increase the penetration of the medicinal substance into the stomach through the epithelial barrier.

The development of targeted local delivery and long-acting drug forms for the eradication of H. pylori is gaining special relevance today. From the local and prolonged action systems in the stomach, high-density, mucoadhesive, floating, swelling systems are considered to be effective forms [14].

Foam systems, which are being offered to the pharmaceutical market as a new generation of independent drug forms, are one of the most successful forms for H. pylori eradication. They have a huge contact surface, a high biological permeability, and a rapid therapeutic effect.

Foams are relatively coarse highly concentrated dispersible gases in a liquid obtained by gas dispersion in the presence of foaming agents. Foams are a dispersion system with a gas dispersion phase, a liquid or a solid dispersion array. Some authors consider foams as a type of emulsion and define it as a highly concentrated heterogeneous system of gas - a liquid in which gas bubbles are divided into thin liquid layers [50].

The theory of foam formation was developed in the late 1970s. The formation of foam is based on complex physicochemical processes, the study of which allows to fully realize the possibility of using its many properties in practical medicine and cosmetology [50].

The foam is thermodynamically unstable. For its formation, the solution must contain at least one component with surfactant properties. The foaming ability of surfactants depends on the structure of their molecule: anion-active surfactants have a high foaming potential compared to cation-active and non-ionogenic substances [50].

The main indicators of foam quality are: foam stability, multiplicity, viscosity, dispersibility, elasticity, penetration ability. Factors affecting the quality of the foam are: concentration of foaming agent, presence of electrolytes, pH, viscosity of the solution, type and concentration of gas, content of additives, stabilizers and moisturizers.The optimal parameters of the foam are: stability - 80.0 - 90.0%, for 20-30 minutes, density - 7-10 g/L [50].

The special advantages of foams in comparison with other therapeutic systems are the following [49,50]:

- As a result of applying foam on the skin and mucous membranes, a mesh is formed that does not completely cover, but discreetly;
- Unlike ointments, diapers, and bandages, foamed skin and mucous membranes are not subjected to pressure. Therefore, these therapeutic forms are offered to cover a significant part of the damaged skin;
- The foam has a protective effect on the surface of burns and wounds and reduces the pain syndrome;

- A little pleasant foam gives the customer emotional pleasure;
- It is distinguished by a high degree of dispersion, large touch surface, high biological penetration and rapid therapeutic effect;
- Foams are light systems, unlike solid medicinal forms, they do not separate out, on the contrary they grow in volume, completely covering the mucous membrane;
- Do not form concentrated solutions at the place of foam formation; do not irritate the mucous membranes;
- The foam provides economical dosing, better contact with the mucous membrane, gives the drug a prolonged action. Under the influence of body temperature increases in volume, fills all free spaces and channels;
- The foam can move in the proximal direction and provide a high concentration of the drug substance for 4 hours;
- Foam is an alternative to solid and liquid formulations that do not require flavor correction and are designed on the one hand to treat the skin and mucous membranes, on the other hand for delivery of medicinal products from the skin and mucous membrane.

The structure-forming components take up one of the most significant places in the foam formulation.Natural polymers and polysaccharides are preferred in both food and pharmaceutical products. Polysaccharides have unique properties for thickening, viscous mass formation, emulsification and stabilization of structurally complex systems [49,50].

A review of the literature shows that the so called "gold standard" of Helicobacter pylori eradication (a combination of antibiotics and proton pump inhibitors) is facing an increasing number of failures and does not have high pharmacotherapeutic efficacy, which illustrates that at the present time the ideal treatment still has not been established.So, the challenge and the goal for the present and future remains to adopt the best available treatment regimen and optimize the treatment of Helicobacter pylori infection. Therefore, it is desirable to search for new natural antimicrobial compounds and develop modified formulations based on them, including foam systems.

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SUMMARY

MEDICATIONS FOR ERADICATION OF HELICOBACTER PYLORI (REVIEW)

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Helicobacter pylori is a pathogenic microorganism that causes gastritis, duodenitis, peptic ulcer disease of the stomach and duodenum. Recent data confirm the close association of Helicobacter pylori with the development of gastric cancer. Due to the failure of standard H. pylori eradication regimens, intensive studies are being conducted to develop targeted local delivery and prolonging activity drug forms.

Based on scientific studies, sufficient knowledge has been accumulated on the inhibitory action of biologically active substances of plant origin: peptides, polyphenols, terpenes, fatty acids on Helicobacter pylori, which allows developing an alternative treatment scheme.

It is especially important today to create local and long-acting, high-density, mucoadhesive, floating and swelling systems. Unlike other forms of medicine, foam systems are interesting in this respect. They are distinguished by a large touch surface, high bioavailability and rapid therapeutic effect. Foam provides economical dosing, better contact with the mucous membrane, and give the drug a prolonged action. Under the influence of body temperature the foam increases in volume, filling all free spaces and channels. However, the foam can provide high concentrations of the medicinal substance for up to 4 hours.

Keywords: Helicobacter pylori, eradication, biologically active substances, medicines and forms.

РЕЗЮМЕ

ЛЕКАРСТВЕННЫЕ СРЕДСТВА ДЛЯ ЭРАДИКАЦИИ HELICOBACTER PYLORI (ОБЗОР)

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Проанализированы ретроспективные и текущие литературные источники по вопросу эффективности препаратов для эрадикации H. pylori. Хеликобактер пилори (Helicobacter pylori) - патогенный микроорганизм, который является причиной гастрита, дуоденита, язвы двенадцатиперстной кишки и желудка. Данные последних лет подтверждают роль Helicobacter pylori в развитии рака желудка. В связи с неудачными стандартными схемами эрадикации H. pylori ведутся интенсивные исследования для создания лекарственных форм пролонгированного действия.

В результате научных исследований накопилось достоточно знаний для использования биологически активных веществ растительного происхождения: пептидов, полифенолов, терпенов, липидовых кислот, характеризующихся подавляющим свойством на H. pylori, что позволяет создать альтернативную схему лечения.

На сегодняшний день актуален вопрос создания системы местного пролонгированного действия в качестве мукоадгезивной, плавающей и набухающей систем. Проведенный анализ выявил, что особый интерес вызывают пенные системы, которые отличаются большой сенсорной поверхностью, высокой биологической проницаемостью и быстрым терапевтическим эффектом, обеспечивают экономичное дозирование, лучший контакт со слизистыми оболочками, придают препарату пролонгированное действие в отличие от других лекарственных средств. Под действием температуры тела пена увеличивается в объеме, заполняя все свободное пространство и каналы. Пена обеспечивает высокую концентрацию лекарственного вещества в течение 4 часов.

რეზიუმე

Helicobacter pylori-ის ერადიკაციის სამკურნალწამლო საშუალებები (მიმოხილვა)

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ჰელიკობაქტერ პილორი (Helicobacter pylori) წარმოადგენს პათოგენურ მიკროორგანიზმს, რომელიც იწვევს გასტრიტს, დუოდენიტს, კუჭისა და თორმეტგოჯა ნაწლავის წყლულოვან დაავადებას. ბოლო წლების მონაცემები ადასტურებს Helicobacter pylori-ის მჭიდრო კავშირს კუჭის კიბოს განვითარებსთან. H. pylori-ის ერადიკაციის სტანდარტული სქემების წარუმატებლობის გამო მიმდინარეობს ინტენსიური კვლევები ადგილობრივი და გახანგრძლივებული მოქმედების წამლის ფორმის შემუშავების მიზნით.

სამეცნიერო კვლევების საფუძველზე დაგროვდა საკმარისი ცოდნა მცენარეული წარმოშობის ბიოლოგიურად აქტიური ნივთიერებების: პეპტიდების, პოლიფენოლების, ტერპენების, ცხიმოვანი მჟავეების დამთრგუნველი მოქმედების Helicobacter pylori-ზე, რაც იძლევა ალტერნატიული მკურნალობის სქემის შემუშავების შესაძლებლობას.

სადღეისოდ განსაკუთრებით აქტუალურია ადგილობრივი და გახანგრძლივებული მოქმედების, მაღალი სიმკვრივის, მუკოადგეზიური, მცურავი, გაჯირჯვებადი სისტემების შექმნა. სხვა სამკურნალწამლო ფორმებისაგან განსხვავებით, ამ მხრივ საინტერესოა ქაფოვანი სისტემები. ისინი გამოირჩევიან დიდი სენსორული ზედაპირით, მაღალი ბიოლოგიური შეღწევადობით და სწრაფი თერაპიული ეფექტით, უზრუნველყოფენ ეკონომიურ დოზირებას, საკმაოდ კარგად შედიან კონტაქტში ლორწოვან გარსთან, ანელებენ წამალს პროლონგირებულ მოქმედებას. სხეულის ტემპერატურის ზეგავლენით ქაფი მატულობს მოცულობაში, ავსებს ყველა თავისუფალ ადგილს და არხს. ამასთან, ქაფს შეუძლია 4 საათის განმავლობაში სამკუნალწამლო ნივთიერების მაღალი კონცენტრაციით უზრუნველყოფა.