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Pathogenesis of Functional Biliary Pain and Pharmacology of Trimebutin

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Aim: to provide data on the pathogenesis of functional biliary pain and provide rationale for the use of trimebutine for this indication.
Key points. Biliary pain is one of the most frequent reasons for patients to see a doctor. The diagnosis of functional disorder of the gallbladder and Oddi's sphincter is legitimate only after the exclusion of organic causes from both the gastrointestinal tract and other organs and systems. The initial appeal to surgeons with a complaint of pain in the epigastrium or right hypochondrium may lead to unjustified surgical intervention that does not bring relief to the patient's suffering. The consequences of cholecystectomy also have an anatomical and physiological justification for the occurrence or preservation of biliary pain. Currently, two main hypotheses are being considered to explain its cause: increased intraluminal pressure due to morphological and functional obstacles to bile outflow and visceral hypersensitivity. In the multilevel system of regulation of the gallbladder and sphincter apparatus, the opioid system occupies a special place. The agonist of peripheral receptors of the enkephalinergic system, trimebutine, in clinical studies led to the relief of biliary pain in more than 80 % of patients with functional biliary disorders, while a significant decrease in the severity of diarrhea, dyspeptic, and constipation syndromes was revealed.
Conclusion. The prescription of the peripheral receptor agonist of the enkephalinergic system, trimebutine, is pathogenetically justified for functional biliary pain.
Keywords: functional disorders, biliary pain, pathogenesis, trimebutine
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Патогенез функциональной билиарной боли и фармакология тримебутина

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Цель: представить данные о патогенезе функциональной билиарной боли и дать обоснование применения тримебутина по данному показанию.
Основные положения. Билиарная боль служит одним из самых частых поводов обращения пациентов к врачу. Диагноз функционального расстройства желчного пузыря и сфинктера Одди правомерен только после исключения органических причин со стороны как желудочно-кишечного тракта, так и других органов и систем. Первичное обращение к хирургам с жалобой на боль в эпигастрии или правом подреберье может привести к необоснованному хирургическому вмешательству, не приносящему облегчения страданиям пациента. Последствия холецистэктомии также создают анатомо-физиологическое обоснование возникновения или сохранения билиарной боли. В настоящее время рассматриваются две основные гипотезы, объясняющие ее причину: повышение внутрипросветного давления из-за морфологических и функциональных препятствий оттоку желчи и висцеральная гиперчувствительность. В многоуровневой системе регуляции работы желчного пузыря и сфинктерного аппарата особое место занимает энкефалинергическая система. Агонист периферических рецепторов энкефалинергической системы тримебутин в клинических исследованиях приводил к купированию билиарной боли более чем у 80 % пациентов с функциональными билиарными расстройствами; одновременно выявлено достоверное уменьшение выраженности диарейного, диспепсического, констипационного синдромов.
Заключение. Назначение агониста периферических рецепторов энкефалинергической системы тримебутина патогенетически обосновано при функциональной билиарной боли.
Ключевые слова: функциональные расстройства, билиарная боль, патогенез, тримебутин
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The relevance of the problem of biliary pain

Biliary pain is one of the most pressing issues in modern clinical practice. The prevalence of biliary disorders, according to most authors, ranges from 12 to 15 % [1–3], and the number of patients tends to increase with age. In conjunction with other functional disorders of the gastrointestinal tract, functional biliary disorders adversely affect the quality of life for patients. Currently, there is a significant variation in the data from various researchers, apparently due to the use of different criteria and diagnostic methods, as well as the heterogeneity of statistically processed groups. For instance, domestic researchers have reported the highest occurrence of functional biliary disorders crossover with irritable bowel syndrome — at 49 % [4].

There is no secret that biliary pain prompts patients to seek surgical consultation, undergo risky instrumental investigations, and sometimes receive unjustified surgical interventions. Surgery, especially in the absence of organic causes, does not always provide complete relief from suffering for the patient. For instance, out of 700,000 cholecystectomies performed annually in the United States, 280,000 patients continue to experience complaints, with functional disorders due to the sphincter of Oddi (SO) occupying the largest niche at 3–40 % [5]. These data are comparable to an approximate estimate for Russia: considering the average frequency of cholecystectomies performed at a rate of 1 per 500–700 people annually, the incidence of SO dysfunction can approximately be around 7–10 per 100,000 population per year [6]. Thus, SO dysfunction can be considered as one of the main causes of biliary pain in patients who have undergone gallbladder removal.

Functional biliary tract disorder

Functional biliary tract disorder is a complex of clinical symptoms that develops as a result of motor-tonic dysfunction of the gallbladder, bile ducts, and sphincters [1]. According to the Rome IV diagnostic criteria, the following variants of functional disorders are identified [7]:

- E1. Biliary pain;
- E1a. Functional gallbladder disorder;
- E1b. Functional sphincter of Oddi disorder of the biliary type;
- E2. Functional sphincter of Oddi disorder of the pancreatic type.

In this classification, biliary pain is isolated (E1) and can be used as a preliminary diagnosis. Within the scope of this literature review, we will examine functional disorders, the primary criteria for which is biliary pain: E1a and E1b.

Signs of biliary pain

It is known that the primary and obligatory manifestation of gallbladder dyskinesia and biliary tract disorders is the occurrence of biliary pain attacks which are localized in the epigastric region or right hypochondrium. These attacks are characterized by the following key features (all of which should be present):

- duration of 30 minutes or more, persistent (rapidly escalating to a plateau);
- it recurs at different intervals (not daily);
- severe, leads to a reduction in the patient's activity; immediate medical attention is often required;
- it is not clearly associated with the intake of antacids or antisecretory agents (disappears in less than 20 % of cases);
- it is not clearly associated with defecation and gas passing;
- it is not clearly associated with the change in body position.

Biliary pain is often accompanied by nausea and vomiting, which provides no relief; irradiation is possible; the pain may be associated with disturbances in sleep patterns (additional non-obligatory signs). Importantly, the diagnosis of typical biliary pain is established under the condition of excluding organic pathology, through careful differential diagnosis of abdominal pain [1, 6, 7].

The signs of functional gallbladder disorder

The presence of typical biliary pain in the absence of gallstones in the gallbladder (or its other organic changes) is a necessary condition for diagnosis of functional gallbladder disorders. Additional confirming signs of this disorder include:

- the reduction in ejection fraction during gallbladder scintigraphy (< 40 %);
- the normal level of liver enzymes, direct bilirubin, amylase, and lipase.

The pathogenesis of functional biliary pain

Currently, two main hypotheses are being considered to explain the cause of biliary pain in gallbladder dysfunction: an increase of intraluminal

pressure due to morphological and functional obstacles to bile outflow, and a visceral hypersensitivity. The primary cause of gallbladder dysfunction is considered to be the presence of the bile oversaturated with cholesterol, due to both irrational nutrition and genetic predisposition. Changes in the state of smooth muscle cells (SMC) and the response to cholecystokinin (CCK) interfere with the relaxation of the gallbladder's neck, hindering the evacuation of its contents. Functional obstruction develops, accompanied by an increase in intraluminal pressure and the onset of biliary pain. The mechanisms of visceral hypersensitivity development and impaired sphincter reactivity are associated, in part, with the effects of lithogenic bile, the influence of low-grade inflammation, and a decrease in sensitivity to CCK. Each stimulus from visceral afferents passes through the enteral nervous system (ENS), is received in the dorsal horns of the spinal cord and is transmitted via supraspinal pathways to the final pain perception in the cerebral cortex. Visceral hypersensitivity manifests as hyperalgesia (increased pain sensitivity) and allodynia (the occurrence of pain in response to stimuli that normally do not cause pain) [1, 7, 8].

In addition to genetic predisposition, an important role in the development of dyskinesia is attributed to lithogenic bile, influenced by dietary habits. In conditions of cholesterol oversaturation, multiple defects in the contractility of the gallbladder are observed. Thus, in a study involving mice on a lithogenic diet, minor hyperplasia of gallbladder's SMC was identified after 2 weeks, more significant morphological changes such as epithelial hyperplasia, pronounced hypertrophy, and thickening of the muscular layer with inflammatory cell infiltration were observed after 4 weeks. After 8 weeks from the start of the study, significant morphological changes, inflammatory infiltration and hypertrophy were noticeable. By the end of the laboratory experiment, spontaneous activity, and asynchrony of gallbladder contractions were predominant [9].

In addition to the above, the literature discusses the role of subtle defects in the bile composition, determining disturbances in the sensitivity of the gallbladder to regulatory hormones (especially to CCK, which normally induces gallbladder contraction and SO relaxation) and the development of its sensory-motor dysfunction. It has been proven that bile oversaturation can initiate microinflammation and disruptions in the so-called 'mucosal homeostasis' of gallbladder. This concept encompasses the structural-functional complex of the mucous membrane, including epithelial cells, including secretory and immune-competent cells, myocytes, blood and lymphatic vessels, nerve endings, and ENS plexuses. There are experimental pieces of evidence implicating several molecules that can link inflammation with motility, with prostaglandin E2 being the most crucial among them [10].

Experimental data on apoptosis of Cajal cells in conditions of bile oversaturation are conspicuous. These cells, present in the gallbladder's SMC, also play a signaling role [11]. This may contribute to an additional disruption in motility. An essential condition for the functioning of the biliary tract is the synchrony and coordination not only of the gallbladder but also of the sphincter apparatus and the duodenum. This coordination is influenced, among other factors, by the functional activity of the migrating motor complex, induced by motilin, a regulatory hormone secreted by enterochromaffin cells of the mucous membrane duodenum and jejunum.

The signs of functional biliary type sphincter of Oddi disorder

The diagnosis of functional biliary type SO disorder is currently justified when the patient presents, as main criteria in addition to typical biliary pain, an elevated level of liver enzymes or dilation of the common bile duct (but not both simultaneously), as well as the absence of stones or other changes in the common bile duct. Additional signs include a normal level of amylase in blood and urine, altered findings in SO manometry and hepatobiliary scintigraphy. The preliminary term 'functional biliary pain' in the algorithm for diagnosing SO dysfunction is acceptable only during the search phase [1, 7]. According to the Rome IV criteria of 2016, the only clinical manifestations which arise after cholecystectomy are now classified as functional disorders of the biliary part of SO. Of the three existing subtypes of SO's biliary part dysfunction that existed previously, only subtype II has been retained, corresponding to an increase in liver enzyme levels or dilation of the common bile duct by more than 10 mm.

Anatomical and physiological consequences of cholecystectomy

The development of SO dysfunction in patients who have undergone this surgical procedure is likely associated with an increase in the volumetric load on the common bile duct (bile deposition) and the SO due to the loss of the reservoir function of the gallbladder. There is evidence that sphincter motility changes after cholecystectomy due to the disruption of the cholecysto-sphincteric reflex. The disruption of this reflex leads to a direct contractile effect of CCK on muscle cells, causing SO obstruction. The cyclic flow of bile

into duodenum is a result of the interaction of all contracting structures in this area, and there is a close reflex and neurohumoral connection between bile-excreting structures and organs in the duodenal zone. Additionally, the role of changes in the rhythm of bile flow into the duodenum is being discussed in relation to the development of duodenogastric reflux [1, 12, 13].

The pathogenesis of functional biliary type sphincter of Oddi disorder

Factors contributing to the development of functional SO disorders include an increase in baseline pressure in the sphincter, leading to impaired bile outflow, intraductal hypertension, and the onset of biliary pain. Even a slight increase in biliary pressure within the physiological range, under conditions of nociceptive sensitization, can enhance nociceptive activity and the perception of pain. The next pathogenetic link is damage to neural regulatory pathways. It has been shown that the relaxing effect of CCK on the SO is suppressed during the immediate postoperative period. This implies a prolonged SO spasm. An important role in the development of dyskinesia is attributed to lithogenic bile. In conditions of cholesterol oversaturation, the contractility of muscle fibers and the perception of signals from the CCK receptor are disrupted (especially with reduced content of hydrophilic fatty acids). Additionally, the passage of bile crystals and microliths can cause repeated trauma to the sphincters, leading to prolonged reflex spasm and the development of chronic subclinical inflammation, under which the response of myocytes to regulatory hormones (CCK, motilin, etc.) is impaired [1, 7].

Enkephalinergic receptors in the regulation system of the biliary tract

Summarizing the above, it can be stated that the ENS is the central element responsible for the formation and transmission of neurohormonal impulses mediating the influence of the central nervous system (CNS) on the gallbladder and SO (Fig. 1). The enkephalinergic system plays a role in regulating the motility and functioning of the ENS.

The ENS serves as a central element ensuring the formation and transmission of neurohormonal impulses mediating the influence of the CNS on the gallbladder and SO. The close neurohumoral interaction between the biliary tract and duodenum determines the motor function of this gastrointestinal tract zone. Multiple factors (genetic, psychosocial, immune-inflammatory, dysmetabolic, hormonal, as well as disruptions in microbiota and "brain — gut" interactions) not only disturb the synchronization of the physiological process, but also distort sensory information, sending these impulses to central structures. Thus, it turns out to be a vicious circle. In this regulatory system of the gallbladder and sphincter apparatus, the enkephalinergic system holds a special place, with its receptors present in both the CNS and the ganglia of the ANS, ENS, and directly in the SMC of the biliary tract.

Pharmacology of trimebutine (Trimedat®) in functional biliary pain

Treating patients with biliary pain is a challenging task for a physician. This is due to the diversity and insufficient understanding of the causes leading to disturbances in the function of the gallbladder and SO, the presence of associated digestive organ diseases in most cases, and the frequent overlap of biliary disorders with functional dyspepsia and/or irritable bowel syndrome, necessitating the simultaneous prescription of multiple medications. Considering that the current proven factors in the onset of symptoms of functional disorders of the gallbladder and SO are visceral hypersensitivity and motor disturbances, the use of trimebutine (Trimedat®) for treating patients with biliary pain is pathogenetically justified. The drug is included in the list of antispasmodic agents in the recommendations of the Russian Gastroenterological Association and in the Rome Consensus for managing such patients.

Being an agonist of peripheral μ-, k-, δ-receptors of the enkephalinergic system in the SMC of the gastrointestinal tract and ENS, the drug exerts a comprehensive effect (Fig. 2).

The drug regulates gastrointestinal motility due to an antispasmodic mechanism (blocks the Na^+ and Ca^{2+} channels of the gastrointestinal tract's SMC, providing a direct spasmolytic effect mediated by normalization of gastrointestinal tract motility and visceral sensitivity). It reduces visceral hypersensitivity by normalizing the expression of 'painful' neurotransmitters in the ENS and blocking the conduction of excessive nociceptive and sensory impulses. Trimebutine also influences the humoral regulation of gastrointestinal tract motility by activating the ENS, promoting the release of gastrointestinal hormones with prokinetic potential (stimulating motilin release, inducing the third phase of the migrating motor complex) [14–17].

Considering the role of inflammation in the pathogenesis of functional disorders of the gallbladder and SO, it is important to note the anti-inflammatory activity of trimebutine (Trimedat®). In 2021, N. Ogawa et al. demonstrated that macrophages pre-treated with trimebutine produced

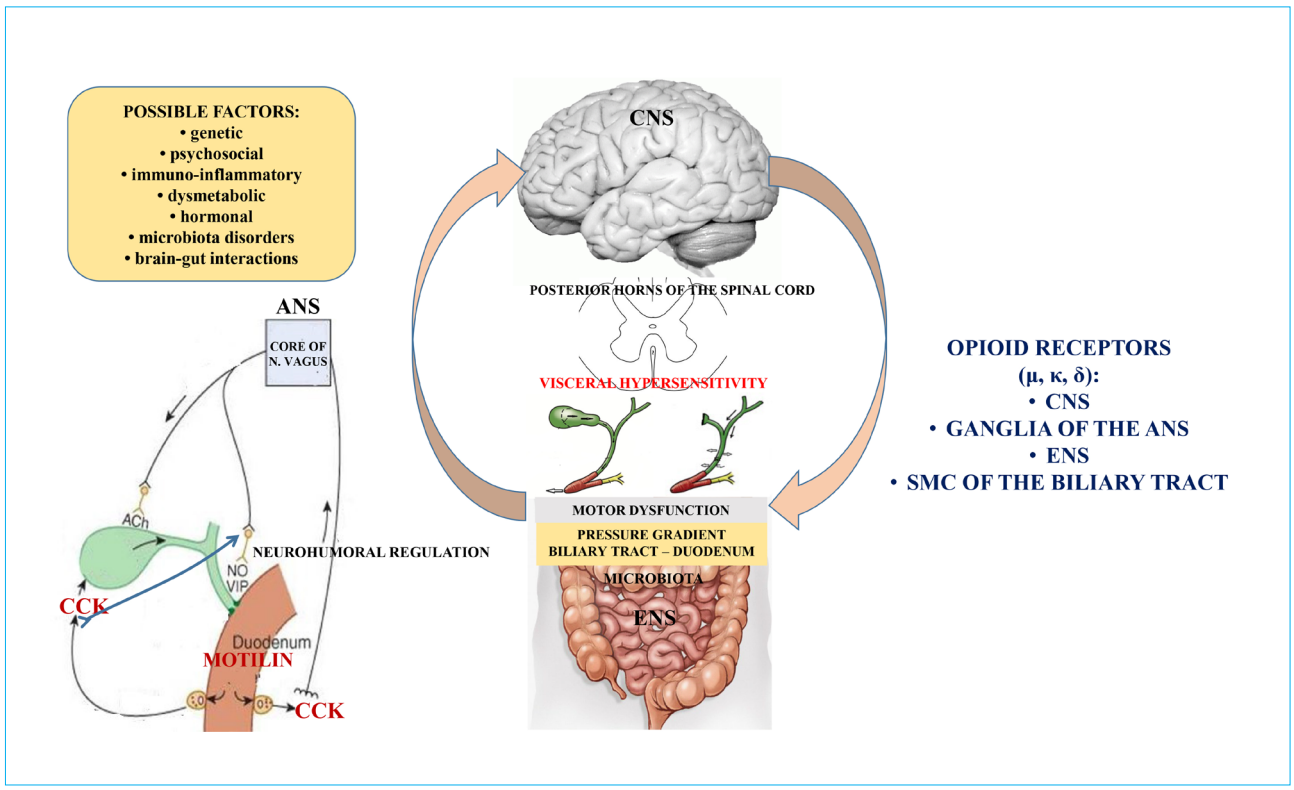

Figure 1. Scheme of multi-level regulation of the work of the gallbladder and sphincter apparatus: ANS — autonomic nervous system; CNS — central nervous system; ENS — enteric nervous system; SMC — smooth muscle cells; CCK— cholecystokinin

Рисунок 1. Схема многоуровневой регуляции работы желчного пузыря и сфинктерного аппарата: ANS — вегетативная нервная система; CNS — центральная нервная система; ENS — энтеральная нервная система; SMC — гладкомышечные клетки; CCK — холецистокинин

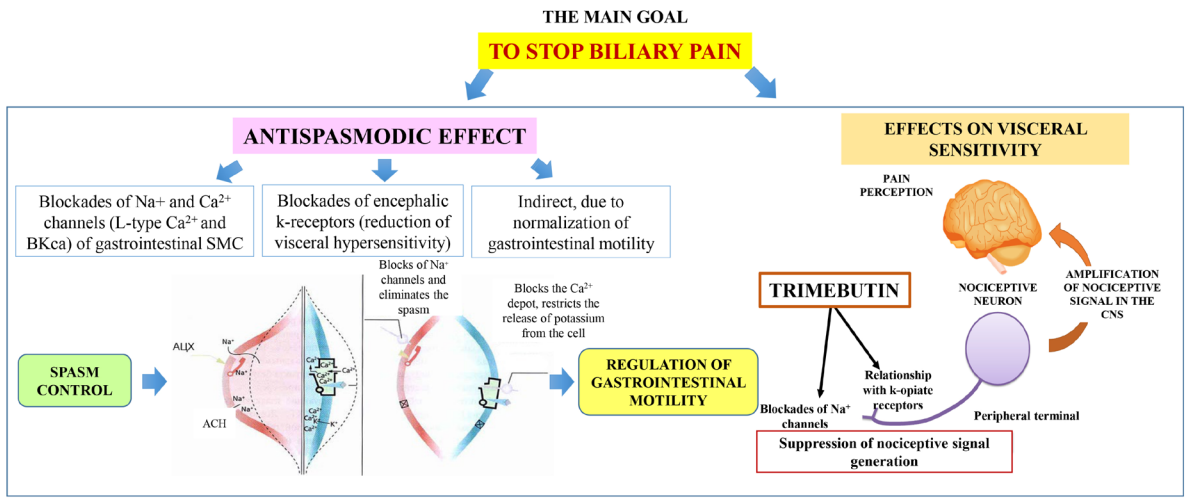

Figure 2. Scheme of the pharmacological action of trimebutine (Trimedat®) for functional biliary pain

Рисунок 2. Схема фармакологического действия тримебутина (Тримедат®) при функциональной билиарной боли

fewer proinflammatory cytokines in response to endotoxin contact. The second part of the experiment demonstrated that administration of trimebutine to mice with endotoxin-induced sepsis led to increased survival rates [18].

The data presented above allows us to consider trimebutine (Trimedat®) not only in the treatment of functional gastrointestinal tract disorders, but also in the comprehensive therapy of other biliary system diseases associated with the presence of an inflammatory component.

The results of some studies confirming the need for the use of trimebutine (Trimedat®) in patients with functional biliary pain are of interest. All these studies were conducted in accordance with the Rome IV criteria, and the main clinical manifestation, pain, persisted for at least the last three months, with a duration of the condition being at least six months. Thus, a domestic study on the efficacy of the medication in 85 patients had demonstrated that a treatment course at a daily dose of 600 mg led to a statistically significant normalization of the motility of the gallbladder and SO, regardless of the initial disorder. Resolution of biliary pain was achieved in 81.2 % of patients with gallbladder and SO disorders and in 98.8 % of patients, the therapeutic effect of trimebutine (Trimedat®) persisted for the subsequent three weeks. Moreover, patients with these functional disorders initially showed a decrease in motilin levels, followed by its significant increase as a result of treatment. A correlation was found between this effect and the normalization of the motor function in the gallbladder and SO, as well as the elimination of duodenogastric reflux [10].

At the Clinic of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology of Sechenov University, an observational program named TRIBUNE (Trimedat® for Biliary Functional diseases patients) was implemented to study the use of trimebutine (Trimedat®) in the routine practice of outpatient and inpatient care for patients (n = 100; 33 % men and 67 % women, average age — 42.2 ± 13.2 years) with functional disorders of the gallbladder and SO. After 28 days of treatment, functional biliary pain was alleviated in the majority of patients. Additionally, a significant reduction in the severity of diarrhea, dyspeptic, and constipation syndromes was observed ($p < 0.0001$). It was also noted that a substantial number of patients with gallbladder dysfunction experienced an increase in the fraction of its emptying, indicating the normalization of bile outflow, presumably due to the normalization of pressure in the duodenum and the tone of the biliary sphincters [14].

The proven efficacy of trimebutine (Trimedat®) in eliminating symptoms in patients with gallbladder and SO disorders in combination with the new anti-inflammatory effect of the molecule makes trimebutine a unique multi-target medication agent.

Conclusion

Functional disorders of the biliary tract, with biliary pain as their main manifestation, pose a significant problem. The high frequency of cholecystectomies, combined with other functional gastrointestinal tract disorders, especially with irritable bowel syndrome, necessitates an individualized approach to patients. It is important to adhere to developed and validated diagnostic algorithms. To alleviate functional biliary pain, the prescription of trimebutine at a daily dose of 600 mg for a 4-week course is pathogenetically justified. Currently, the booster form allows the medication to be taken twice a day instead of three times, achieving normalization of motility and reduction of visceral hypersensitivity.

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