https://doi.org/10.22416/1382-4376-2021-31-5-34-50

Hymecromone Administration in Real Clinical Practice: Results of the Prospective Multicentre Observational Study in the Republic of Kazakhstan

Alexander V. Nersesov[1], Dzhamilya A. Kaybullaeva[1], Venera S. Rakhmetova[2], Irina A. Lozinskaya[3], Asem K. Kurmangalieva[4], Venera S. Ayupova[5], Aida B. Orazbaeva[6], Ayzhan K. Kanabaeva[7], Yuliya O. Shulpekova[8,*]

[1] *Asfendiyarov Kazakh National Medical University, Almaty, Republic of Kazakhstan*
[2] *Astana Medical University, Nur-Sultan, Republic of Kazakhstan*
[3] *Regional Clinical Hospital, Karaganda, Republic of Kazakhstan*
[4] *Regional Clinical Hospital, Chimkent, Republic of Kazakhstan*
[5] *City Outpatient Clinic No. 5, Almaty, Republic of Kazakhstan*
[6] *ICLINIC Medical Centre, Nur-Sultan, Republic of Kazakhstan*
[7] *"Beta i K" Medical Centre LLP, Almaty, Republic of Kazakhstan*
[8] *Sechenov First Moscow State Medical University (Sechenov University), Moscow , Russian Federation*

Introduction. This multicentre prospective non-interventional observational study was conducted to obtain additional data about Odeston efficacy and safety in routine clinical practice. The objectives of the study included collection of clinical characteristics of patients, evaluation of Odeston effects in treatment of biliary pain and changes in the gallbladder emptying, evaluation of compliance to therapy, and treatment effect satisfaction.

Materials and methods. The study was conducted from July 2020 to April 2021 at the premises of 60 study sites in 4 cities of the Republic of Kazakhstan. Patients having indications for Odeston administration according to the patient leaflet were enrolled. The study included 2 patient visits and an intermediate telephone contact. A visual analogue scale and RAPID questionnaire were used to characterise biliary pain; severity of associated symptoms, bowel habit and a quality of life according the SF-12 were also assessed. A rate of a ≥50 % reduction in symptom severity was used as a primary efficacy criterion; a rate of a ≥10 improvement in the SF-12 quality of life score was used as a secondary efficacy criterion. Compliance to treatment was evaluated using a number of days on Odeston. Treatment satisfaction was assessed using 5 grades.

Results. 877 patients, 68.2 % of females and 31.8 % of males, were included in the study; the mean age was 46.0 ± 14.9 years. Primary functional biliary disorder was diagnosed in 65.3 % of patients, chronic non-calculous cholecystitis — 51.4 %, uncomplicated gallbladder disease — in 8.9 %, biliary sludge — 38.4 %, sphincter of Oddi functional disorder — 5.3 % of patients. A dose of Odeston was prescribed at the discretion of the physician. Group A patients received 600 mg (n = 89), group B received 1200 mg of Odeston a day (n = 788). In group B, an incidence of pronounced pain interference with daily living activities was higher. In both groups, the mean VAS scores were reduced to 1 point on treatment, a primary efficacy criterion was achieved in 77.3 % of patients in group A and in 79.8 % of patients in group B, $p < 0.05$. In both groups, a reduction in the incidence of constipation and diarrhea ($p < 0,001$) and an increase in the mean scores of physical and mental functioning were noted ($p < 0.001$, though a secondary efficacy criterion was not achieved (a ≥10 change in the SF-12 score). A prevalence of ultrasonographic sings of biliary sludge was reduced, and an increased gallbladder emptying was observed ($p < 0.001$). 77.4 % of patients in a total group of patients reported about drug administration for 21 days. A number of patients who were completely satisfied with treatment was higher in group B ($p = 0.027$).

Conclusions. It was found that biliary pain interfered with daily living activities and commonly accompanied by other symptoms of gastrointestinal dysmotility. Odeston effectively reduces the severity of biliary pain, corrects dyspeptic disorders and normalizes stool pattern in patients with functional and organic diseases of the biliary system. Treatment satisfaction was higher with a dose of 1200 mg a day, particularly in more pronounced interference of pain with daily living activities.

Key words: functional biliary disorders, chronic non-calculous cholecystitis, biliary pain, hymecromone

Conflict of interests. The publication was prepared with the support of JSC "Adamed Pharma" in the Republic of Kazakhstan.

For citation: Nersesov A.V., Kaybullaeva D.A., Rakhmetova V.S., Lozinskaya I.A., Kurmangalieva A.K., Ayupova V.S., Orazbaeva A.B., Kanabaeva A.K., Shulpekova Yu.O. Hymecromone Administration in Real Clinical Practice: Results of the Prospective Multicentre Observational Study in the Republic of Kazakhstan. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2021;31(5):34–50. https://doi.org/10.22416/1382-4376-2021-31-5-34-50

Опыт применения гимекромона в условиях реальной клинической практики: результаты проспективного многоцентрового наблюдательного исследования в Республике Казахстан

А.В. Нерсесов[1], Д.А. Кайбуллаева[1], В.С. Рахметова[2], И.А. Лозинская[3], А.К. Курмангалиева[4], В.С. Аюпова[5], А.Б. Оразбаева[6], А.К. Канабаева[7], Ю.О. Шульпекова[8,*]

[1] НАО «Казахский национальный медицинский университет» имени С.Д. Асфендиярова, Алма-Ата, Республика Казахстан

[2] НАО «Медицинский университет города Астана», Нур-Султан, Республика Казахстан

[3] КГП «Областная клиническая больница, Караганда» Управления здравоохранения Карагандинской области, Республика Казахстан

[4] Областная клиническая больница, Чимкент, Республика Казахстан

[5] Городская поликлиника № 5, Алма-Ата, Республика Казахстан

[6] Медицинский центр ICLINIC, Нур-Султан, Республика Казахстан

[7] Медицинский центр ТОО «Бета и К», Алма-Ата, Республика Казахстан

[8] ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» (Сеченовский Университет) Министерства здравоохранения Российской Федерации, Москва, Российская Федерация

Цель. Настоящее многоцентровое проспективное неинтервенционное наблюдательное исследование проведено с целью получения дополнительных данных об эффективности и безопасности применения препарата гимекромон (Одестон) в повседневной клинической практике. В задачи исследования входили клиническая характеристика пациентов, оценка действия Одестона в лечении билиарной боли и изменении показателей опорожнения желчного пузыря, оценка приверженности к терапии и удовлетворенности эффектом лечения.
Материалы и методы. Исследование проводилось с июля 2020 по апрель 2021 г. на базе 60 исследовательских центров в 4 городах Республики Казахстан. В исследование включали пациентов с наличием показаний к назначению Одестона в соответствии с инструкцией по применению. Были предусмотрены 2 визита пациента и промежуточный контакт по телефону. Для характеристики билиарной боли применялись визуальная аналоговая шкала (ВАШ) и опросник Routine Assessment of Patient Index Data (RAPID); также анализировали выраженность сопутствующих симптомов, характер стула, качество жизни по опроснику Short Form Survey-12 (SF-12). В качестве первичного критерия эффективности принята доля случаев снижения выраженности симптомов ≥50 %; вторичного критерия эффективности — доля случаев повышения оценки качества жизни по SF-12≥10 баллов. Приверженность к лечению оценена по числу дней приема Одестона. Удовлетворенность лечением оценена по 5 градациям от «полностью удовлетворен», до «полностью не удовлетворен».
Результаты. В исследование включены 877 пациентов, 68,2 % женщин и 31,8 % мужчин; средний возраст 46,0 ± 14,9 года. Диагноз первичного функционального билиарного расстройства установлен у 65,3 % пациентов, хронический бескаменный холецистит — 51,4 %, неосложненная желчнокаменная болезнь (ЖКБ) — 8,9 %, билиарный сладж — 38,4 %, функциональное расстройство сфинктера Одди — 5,3 % пациентов. Доза Одестона назначалась по усмотрению врача. В группе А пациенты получали 600 мг (n = 89), в группе В — 1200 мг Одестона в сутки (n = 788). В группе В отмечено больше случаев отчетливого влияния боли на повседневную активность. В обеих группах на фоне лечения средние показатели ВАШ уменьшились до 1 балла, первичный критерий эффективности терапии достигнут в группе А у 77,3 %, в группе В — у 79,8 % (p < 0,05). В обеих группах отмечено уменьшение доли случаев запора и диареи (p < 0,001), повышение средних показателей физического и ментального функционирования (p < 0,001), хотя не установлен вторичный критерий эффективности (изменение показателя SF-12≥10 баллов). По данным УЗИ, уменьшилась частота выявления билиарного сладжа, отмечено увеличение степени опорожнения желчного пузыря (p < 0,001). 77,4 % пациентов общей группы сообщили о приеме препарата на протяжении 21 дня. Количество пациентов, полностью удовлетворенных лечением, было больше в группе В (p = 0,027).
Выводы. Установлено влияние билиарной боли на повседневную активность, частое сочетание билиарной боли с другими симптомами нарушения моторики пищеварительного тракта. Показана достаточно высокая эффективность Одестона в лечении билиарной боли, коррекции диспепсических расстройств и нарушении стула, более высокая удовлетворенность лечением при назначении дозы 1200 мг в сутки, особенно при более выраженном влиянии боли на повседневную активность.

Ключевые слова: функциональные билиарные расстройства, хронический бескаменный холецистит, билиарная боль, гимекромон
Конфликт интересов: Публикация подготовлена при поддержке АО «Адамед Фарма» в Республике Казахстан.

Для цитирования: Нерсесов А.В., Кайбуллаева Д.А., Рахметова В.С., Лозинская И.А., Курмангалиева А.К., Аюпова В.С., Оразбаева А.Б., Канабаева А.К., Шульпекова Ю.О. Опыт применения гимекромона в условиях реальной клинической практики: результаты проспективного многоцентрового наблюдательного исследования в Республике Казахстан. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2021;31(5):34–50. https://doi.org/10.22416/1382-4376-2021-31-5-34-50

Introduction

Biliary disorder is one of the most common reasons for patients to visit a gastroenterologist, physician, or general practitioner.

The prevalence of primary functional gallbladder disorder and sphincter of Oddi disorder is about 5–10 %. Due to development of the Rome Diagnostic Criteria for Functional Biliary Disorders [1], a view of this problem gets more consistent. However, until now somewhat obsolete approaches to diagnostics and diagnosis formulation are prevalent in real practice (e.g., "chronic non-calculous cholecystitis"), resulting in a complicated comparison of data on the prevalence and treatment efficacy of biliary dysfunctions. Based on contemporary insights, impaired bile outflow because of abnormal relaxation of the cystic duct sphincter and sphincter of Oddi and impaired gallbladder emptying are the main causes of pain attacks in functional biliary disorders. Such changes are explained by impaired responsiveness to cholecystokinin, local reflexes, and low degree inflammation [2]. Pain may be accompanied by nausea and vomiting, but it is not a classic biliary colic which is typical for gallstone disease (GSD). Functional biliary disorders may be present together with dysmotility of other gastrointestinal organs, thus, explaining dyspeptic symptoms and intestinal dysfunction in such patients [3, 4].

In prevalence of GSD in he Eurasian population is about 10 %. Though GSD is predominantly characterized by an uncomplicated course (without attacks of colic, and acute cholecystitis due to mechanical biliary obstruction), this disease is commonly accompanied by dyspeptic symptoms which can be explained by adjacent organ dysmotility and inadequate bile outflow during digestion. In uncomplicated GSD, bloating and postprandial fullness, nausea, duodenogastric and gastroesophageal reflux, excessive gas after fatty food are commonly reported, and abnormal bowel pattern is possible [5].

Some investigators consider biliary sludge as the initial stage of GSD, however, in most cases it is most likely a separate syndrome because of non-progressive course in 40 % and complete reversibility in 40 % of cases. Biliary sludge is associated with impaired gallbladder emptying in the setting of high bile lithogenicity and mycin hyperproduction. Biliary pain in sludge can be caused by impaired bile outflow because of obstruction with bile crystals or impaired sphincter relaxation [6].

The sphincter of Oddi functional disorder is mainly associated with prior cholecystectomy, impaired cystic and sphincter reflexes, increased volume load on the common bile duct, and the passage of bile crystals. This disease is reported in about 1.5 % of patients after cholecystectomy and is much more common in women [1, 7].

While the main causes of pain attacks in the above-described biliary diseases are considered to be a sphincters hypertonicity ("functional obstruction") or a passage of bile crystals (elements of mechanical obstruction), different classes of spasmolytics, sometimes in combination with ursodeoxycholic acid, are used for treatment. Most selective "biliary" spasmolytics should be favoured to reduce the risk of systemic adverse effects.

Hymecromone (Odeston), a synthetic derivative of umbelliferone contained in many medicinal herbs, possesses highly selective spasmolytic activity in the biliary tree. After oral administration, hymecromone is absorbed in the proximal small intestine and transferred through the portal vein to the liver where it is uptaken by organic anion transporting protein 2 (OATP 2) on the hepatocyte basolateral membrane. Intracellularly hymecromone is bound to glucuronic acid, and exported into bile by multidrug resistance-associated protein 2 (MRP2) accompanying with sodium and potassium secretion and water diffusion [8]. While delivered into proximal small intestine, hymecromone is involved in enterohepatic circulation (not more than 3 % of the active substance reaches the systemic circulation after the first-pass metabolism). A highly selective action on the bile ducts is explained by such pharmacokinetic profile.

Antispasmodic action is the most significant effect of hymecromone (Odeston). Experiments showed smooth myocytes relaxation under the influence of hymecromone was realized in the presence of NO-synthase, i.e. probably via an increase in cGMP level [9, 10]. It is reported also that coumarin derivatives, to which hymecromone belongs, block potassium channels linked to acetylcholine receptor [11]. The medicine does not directly interact with acetylcholine receptors [9].

Hymecromone effect was studied in clinical and experimental works, including studies in functional biliary disorders and in patients after cholecystectomy [12–15]. Based on the results of these works, it can be concluded that the medication improves bile outflow through the sphincter of Oddi and effectively relieves biliary pain of functional (non-inflammatory and non-neoplastic) origin. Hymecromone does not enhance the gallbladder contractile function which makes it safe in GSD [16]. The medication can be combined with ursodeoxycholic acid to reduce bile lithogenicity and provide more effective litholysis. A significant effect of such combination was shown

in the treatment of biliary sludge [17]. A cross-over placebo-controlled study showed the effect of hymecromone in resolving dyspeptic disorders commonly accompanying biliary disorders [18].

A purpose of this study analysis of the experience of gimecromone application (Odeston, manufactured by JSC Adamed Pharma, Poland, RK-LS-5 No. 012938 dated October 26, 2018) by practitioners of the Republic of Kazakhstan in order to concretize data on the drug effectiveness and safety.

The tasks of the study included evaluation of Odeston antispasmodic effect in relieving biliary pain in clinically diverse groups of patients, evaluation of the patient compliance to therapy and patient satisfaction with treatment after 21 days of therapy.

Materials and methods

The study was designed as a multicentre prospective non-interventional observational and conducted between July 2020 and April 2021 at the premises of 60 study sites in 4 big cities of the Republic of Kazakhstan: Nur-Sultan, Almaty, Karaganda, Shymkent. The protocol was consistent with Orders of the Ministry of Health of the Republic of Kazakhstan No. 142 dated 2 April 2018 "On Approval of Rules for Conducting Pre-Clinical (Non-Clinical) Studies, Clinical Studies, Clinical Laboratory Evaluation of Medical Devices for In Vitro Diagnostics, and Requirements to Pre-Clinical and Clinical Bases", No. KR DSM-310/2020 dated 21 December 2020 "On Approval of Rules for Conducting Biomedical Studies and Requirements to Study Sites", and with the World Medical Association Declaration of Helsinki. The study was approved by the Central Bioethics Committee at the Ministry of Health of the Republic of Kazakhstan (Excerpt from Minutes No. 8 dated 29 June 2020), local ethics committees at the healthcare facilities which participated in this clinical study. A list of study doctors (general practitioners, physicians, gastroenterologists) was randomly generated.

Male and female patients aged 18–65 years old having indications for Odeston (hymecromone) administration according to the patient information leaflet: primary functional disorder of the gallbladder or the sphincter of Oddi, secondary biliary dysfunction due to uncomplicated GSD, biliary sludge, chronic acalculous cholecystitis, functional disorder of the sphincter of Oddi after a cholecystectomy ("a post-cholecystectomy syndrome") were enrolled.

Patients with contraindications listed in the patient information leaflet for Odeston (hypersensitivity to the drug product, bile duct obstruction; renal/hepatic insufficiency, inflammatory bowel diseases, ulcer disease, hemophilia), patients suffering from cholangitis, decompensated diabetes mellitus, pregnant or breastfeeding women, patients addicted to alcohol and psychotropic substances, patients with aggravation of mental disorders or any chronic disease, requiring urgent care; patients with diseases or abnormalities according to the laboratory and instrumental examination, which, in the doctor's opinion, could affect the treatment safety and patient compliance to Odeston administration or require prescription of medicines prohibited in the study; and patients who participated in other clinical studies within 3 months prior inclusion in this study were excluded.

Prohibited medications in the study included morphine and other opioid analgesics, prokinetics, other classes of spasmolytics (including nitrates, calcium channel blockers, myotropic spasmolytics, anticholinergic agents), indirect anticoagulants. Other medicinal products including ursodeoxycholic acid and antisecretory agents referred to permitted therapy.

The study included an enrollment stage coincident with Visit 1, subsequent Visit 2, and intermediate telephone contact (Fig. 1). A 10-point visual analogue scale (VAS) with 0 rating as "no pain" and 10 rating as "the highest severity of pain" was used to assess biliary pain severity; a patient should rate a severity of attacks of right upper quadrant abdominal pain for 1 minute. Interference of pain with daily living activities was assessed using the RAPID questionnaire (Routine Assessment of Patient Index Data) with a score of ≤5 rating as "no significant interference with daily living activities", a score of 6–10 indicates a "minor limitation in activities, a score of 11–20 — "moderate limitation in activities", and a score of ≥21 — "significant limitation in activities". Besides, a severity of concomitant symptoms (heartburn, bitter taste in mouth, nausea, bloating, abdominal pain) using 5-point Likert scale, the quality of life using the SF-12 (Short Form Survey-12), and stool consistency using the Bristol Stool Form scale were analysed.

A percentage of patients who achieved a ≥50 % reduction in severity of pain and other symptoms from baseline and improvement of ultrasound characteristics of the bile ducts were used as *primary efficacy criteria*. *A secondary efficacy criterion* was an assessment of the percentage of patients with a clinically significant (a score of ≥10) improvement of the quality of life on the SF-12.

Compliance to treatment was assessed using patient reported data (number of days on Odeston). A ≥ 90 % completion of a 21-day therapy was considered as a criterion of high compliance to treatment. Patient *satisfaction* with treatment was assessed using 5 grades: "completely satisfied", "more likely satisfied", "neither satisfied, nor unsatisfied", "more likely unsatisfied", "completely unsatisfied".

At Visit 1, a study doctor made a decision about patient inclusion (enrollment) in the study based on the available clinical data and indications for Odeston administration — primary functional biliary disorders or bile duct dysfunction due to

uncomplicated GSD, biliary sludge. When establishing diagnosis of primary functional biliary disorders, treating physicians relied on the diagnostic criteria provided in Rome IV consensus [1]. Such factors as smoking status and presence of psychoemotional disorders were evaluated in patients; menstrual cyclicity /menopause, administration of contraception, hormonal replacement therapy were recorded for women. Besides, at Visit 1, demographic characteristics, vital signs (body weight, height, BMI, body temperature) were recorded. The objective instruments such as a 10-point VAS to assess biliary pain and the RAPID questionnaire (Routine Assessment of Patient Index Data) to assess pain interference with daily living activities were used. The SF-12 (Short Form Survey-12) quality of life questionnaire was also used. A severity of concomitant symptoms (heartburn, bitter taste in mouth, nausea, bloating, abdominal pain) was assessed using a 7-point Likert scale, and stool consistency was assessed using the Bristol scale. Concomitant medications and prior laboratory examination results such as hematology and blood chemistry test measuring levels of AST, ALT, ALP, bilirubin, glucose, lipid fractions were recorded. For objectivization of therapy results in the absence of gallstones in patients, an ultrasound examination after a choleretic breakfast was used: assessment of the gallbladder emptying degree 10, 15, 30 minutes after breakfast.

Treatment with Odeston 200 or 400 mg 3 times a day half an hour before meals (600 or 1200 mg a day) was prescribed to patients for 21 days (according to the local patient information leaflet). Odeston dose was selected at the discretion of the study doctor mainly based on the pain severity and degree of its interference with daily activities.

An intermediate telephone contact with a patient took place on Day 10 ± 5 after initiation of Odeston treatment. At the same time, continuation or discontinuation of the drug therapy and possible adverse events (AEs) were recorded.

At Visit 2 ("end of treatment" — Day 21 ± 5) treatment with Odeston was discontinued. At this visit, a number of patients completed a 21-day therapy was recorded. Physical examination, assessment of patient complaints, biliary pain severity on the VAS, concomitant symptoms, stool consistency, concomitant therapy, possible AEs, and the SF-12 completion were conducted. Patient compliance to treatment based on the patient reported data (number of days on Odeston) and patient satisfaction with treatment were assessed. In patients who completed Odeston therapy according to a recommended scheme (21 ± 5 days), an ultrasound of the gallbladder and bile duct functional state was performed after a choleretic breakfast.

Statistical processing. The Student unpaired t-test was used for continuous variables to compare the results in two groups; the chi-square test was used to assess a statistical relationship between a treatment scheme and smoking status; a frequency comparative analysis of proportions (percentages) using the Fisher exact test was used to assess a statistical relationship between a treatment scheme and all nominal variables. Data processing and all statistical calculations for this protocol were performed in SAS-9.4 statistical package.

A total of 877 patients were selected to participate in the study (Fig. 1). Based on the prescribed dose of Odeston, all patients were allocated to two groups: group A — Odeston 600 mg a day (n = 89) group B — Odeston 1200 mg a day (n = 788). Treatment outcomes and observations of these patients were used for analysis of the efficacy, safety, and compliance to therapy.

Study results

Demographic and clinical characteristics of the study groups. 877 patients, of them 598 (68.2 %) women and 279 (31.8 %) men, were included in the study; the mean age of the patients was 46.0 ± 14.9 years. The patients were under outpatient supervision of general practitioners and physicians (in 77 % of cases) and gastroenterologists (in 23 % of cases)

Primary functional biliary disorder was diagnosed in 573 (65.3 %) patients, chronical non-calculous cholecystitis — in 451 (51.4 %), uncomplicated GSD with biliary tract dysfunction — in 77 (8.9 %), biliary sludge — 337 (38.4 %), sphincter of Oddi dysfunction after cholecystectomy (also referred to as PCS) — 47 (5.3 %) patients.

Thus, a combination of diseases or syndromes was detected in a significant percentage of patients, it was mostly a combination of "primary functional biliary disorder" and "chronic non-calculous cholecystitis", and "biliary sludge". Such situations could be associated with pre-existing diagnosis of "chronic non-calculous cholecystitis" in medical records or biliary sludge detected at routine examination.

Analysis of a social status showed that 744 (84.8 %) patients were married, and 133 (15.2 %) were single during the study. 502 (57.2 %) patients had higher education, 370 (41.9 %) had incomplete higher education or secondary vocational education. Depending on the work-related activity, the study participants were classified as follows: 306 (34.9 %) patients had jobs demanding low physical activity, 93 (10.6 %) and 11 (1.3 %) patients had jobs demanding moderate and high physical activity, respectively, and 467 (53.2 %) patients were mental workers. During participation in the study, 126 (14.4 %) patients were current smokers, 132 (15.1 %) were ex-smokers, and 619 (70.6 %) patients never smoked.

178 (29.7 %) women were menopausal, 420 (70.3 %) women had menstrual periods preserved. 38 and 12 women (6.4 % and 1.4 % in a total

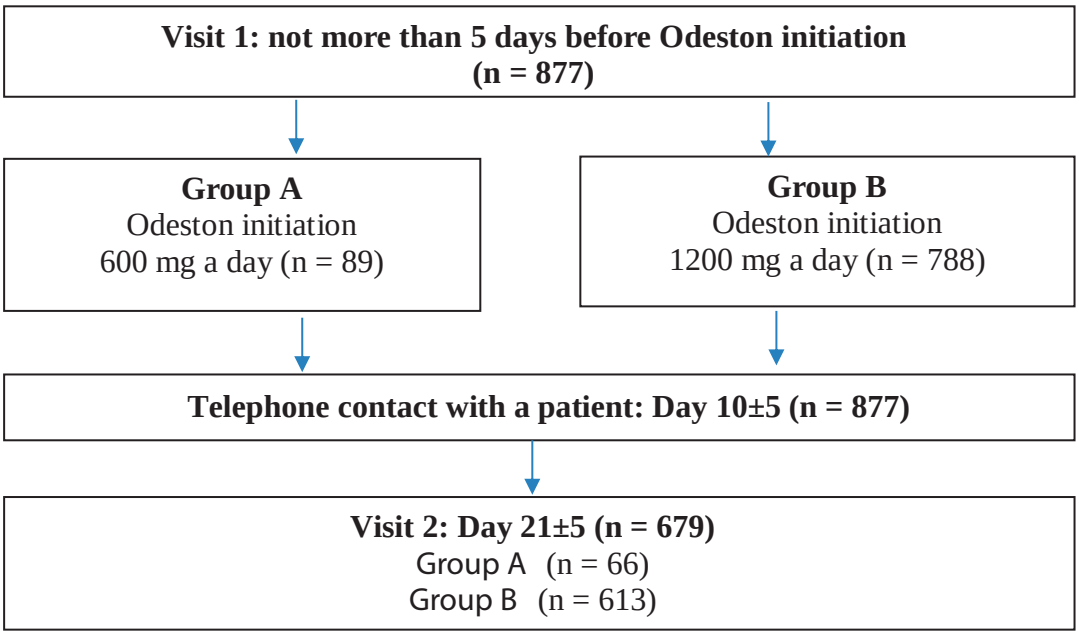

Fig. 1. Patient distribution in the study

population of patients) administered oral contraceptives and hormonal replacement therapy.

Mental illnesses (schizophrenia, anxiety and depressive cognitive disorders) were diagnosed in 20 (2.3 %) participants.

137 (15.6 %) patients received prior (more than 3 weeks before inclusion in this study) therapy with hymecromone, 557 (63.5 %) patients previously received miotropic spasmolytics, 81 (9.2 %) — anticholinergic drugs, 277 (31.6 %) — ursodeoxycholic acid, 195 (22.2 %) — non-steroidal anti-inflammatory agents, 14 (1.6 %) — opioid analgesics, and 133 (15.2 %) patients received prior treatment with antimicrobial drugs.

Therapy with Odeston was prescribed to all patients at Visit 1 because of occurrence of biliary pain episodes and dyspeptic disorders; a treating physician, at his/her discretion, selected a dose of 600 mg or 1200 mg, it was recommended to administer the medicinal product for 21 days.

To compare the efficacy and safety of two treatment regimens, patients were divided into 2 groups: patients receiving hymecromone 200 mg 3 times a day (Group A, $n = 89$) and patients receiving hymecromone 400 mg 3 times a day (Group B, $n = 788$). Thus, Odeston in a daily dose of 600 mg was administered in 10.1 % of cases, and a 1200 mg dose was administered in 89.9 %. Groups were consistent for the patient age and gender (group A: mean age 46.6 ± 16.1 years, 28 (31.5 %) men; group B: mean age 46 ± 14.8 years, 251 (31.9 %) men, $p < 0.05$). There were no significant between-group differences in smoking status, mental disorder incidence ($p < 0.05$). A vast majority of patients in both groups were mental workers or had jobs demanding low physical activity ($n = 773$ (88.1 %)). Besides, no significant differences in hormonal status of women (menstrual cyclicity, menopause, use of contraception and hormonal replacement therapy) were found ($p = 0.786$, $p = 0.102$, $p = 0.344$, $p = 1.0$, respectively). No differences in treatment for the previous year: administration of hymecromone ($p = 0.646$), ursodeoxycholic acid ($p = 0.279$), spasmolytics ($p = 0.203$), anticholinergic agents ($p = 0.080$), non-steroidal anti-inflammatory drugs ($p = 0.106$), antimicrobial agents (p = 0.436) were found as well. A mean body mass index of the patients was 25.3 ± 4.1 kg/m^2. Obesity (body mass index ≥ 30 kg/m^2) was determined in 91 (10.4 %) patients of the total population: in 11 (12.4 %) patients in group A and 80 (10.2 %) patients in group B with no significant differences ($p = 0.468$).

A nosological pattern reflecting indications for administration of hymecromone (Odeston) in groups A and B at Visit 1 is shown in Figure 2. In group A, primary functional biliary disorders, biliary tract dysfunction due to GSD and sphincter of Oddi dysfunction after a cholecystectomy were diagnosed with a significantly higher rate ($p < 0.001$, <0.001, and 0.021, respectively).

Concomitant therapy. A frequency of concomitant therapy administration concurrently with treatment with Odeston is shown in Table 1. In the vast majority of cases, the patients had already received the medication to which Odeston was added. A difference lied in a more frequent administration of ursodeoxycholic acid in group A patients.

Before therapy with hymecromone (Visit 1), a VAS score of biliary pain severity corresponded, on average, to 5 points in both groups (Fig. 3).

Interference of biliary pain with daily living activities was assessed on the RAPID scale. A significant

prevalence of mild cases with no pain interference with daily living activities (grade 1) was noted in group A, while group B had significantly more cases of pronounced pain interference (grades 2 and 3), $p < 0.001$ (Fig. 4).

In addition to biliary pain, the patients also had concurrent dyspeptic signs evidencing upper gastrointestinal motility disorder (commonly referred to as "biliary dyspepsia symptoms"). A baseline severity of such symptoms in groups A and B is shown in Figure 5. In group B, a significantly higher incidence of pronounce bitter taste in mouth (scored as 3–5 points, $p = 0.022$) was reported. Comparison of other symptoms such as bloating, nausea, heartburn, abdominal pain showed insignificant between-group differences in severity.

Bowel habit was assessed using the Bristol scale (Fig. 6). Normal stool consistency before therapy with Odeston was noted only in one third of patients in both groups. The incidence of unformed stool and constipation in groups A and B did not significantly differ.

At the beginning of treatment, the most of patients had complete blood count and blood chemistry test done. In group B, there was a significantly higher white blood cell count, though a mean count was within normal range (7.3 ± 2.7 versus 5.9 ± 1.6, $p < 0.001$), and higher activities of alkaline phosphatase (42.6 ± 41 versus 64.7 ± 48.1, $p < 0.001$), gamma-glutamyl transpeptidase (21.7 ± 23.3 versus 31.9 ± 17.6, $p < 0.001$), conjugated bilirubin (5.5 ± 5.4 versus 7.7 ± 7.2, $p = 0.014$), and unconjugated bilirubin (7.4 ± 7.5 versus 9.2 ± 6.2, $p = 0.029$). A slight increase in conjugated bilirubin level was noted in some patients, however, no signs of mechanical obstruction were present. A serum lipid profile in group B showed higher LDL (1.8 ± 1.3 versus 2.5 ± 1.7, $p = 0.001$) and HDL levels (1.4 ± 2.1 versus 1.7 ± 0.9, $p = 0.019$). Glycemic and lipid profile assessment based on a nosological form showed higher levels of triglycerides, LDL, and HDL in patients with secondary biliary dysfunction (due to chronic non-calculous cholecystitis, GSD, sludge and after a cholecystectomy for GSD) compared to patients with primary dysfunction (Fig. 7).

Liver and bile duct ultrasound and ultrasonic cholecystography findings. At Visit 1, ultrasound findings were assessed in 877 cases. Ultrasound cholecystography was performed for 48 patients without gallbladder stones (group A — 7 patients (14.6 %), group B — 41 patients (85.4 %)) at Visits 1 and 2. At Baseline, 29 (60.4 %) had increased echogenicity of the liver, 13 (27.1 %) had heterogeneous echostructure, and 12 (25 %) patients had attenuated vascular markings. Ursodeoxycholic acid was prescribed concomitantly with Odeston to all patients with biliary sludge. A high percentage of patients (66.7 %) in a total group had bile echo-heterogeneity events and biliary sludge (Fig. 8).

Odeston treatment outcomes. At Visit 2, a part of patients was excluded from analysis due to early withdrawal of Odeston by patients. A number of patients was decreased to 66 (74.2 % of the initial number) in group A and to 613 (77.8 % of the initial number) in group B. Compared to Visit 1 (Fig. 2), a nosological structure of groups did not fundamentally change, and a rate of primary functional biliary disorder and biliary dysfunction due to uncomplicated GSD remained much higher in group A ($p = 0.001$, Fig. 9).

At Visit 2, a VAS mean score of biliary pain severity was decreased to 1 in both groups ($p < 0.001$ compared

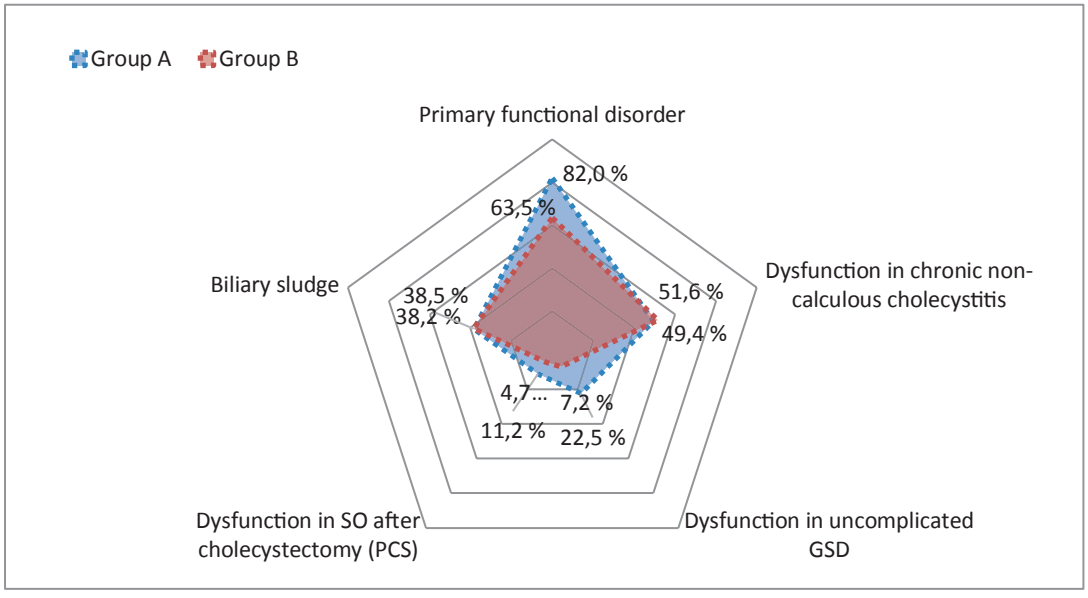

Fig. 2. A pattern of indications for Odeston administration in groups A and B. A diagram shows a rate of different diseases of the bile ducts in patients who participated in the study. Group A marked by blue, and group B — by red

Table 1. Concomitant therapy

Concomitant treatment	Group A (n = 89)	Group B (n = 788)	p
Ursodeoxycholic acid, n (%)	66 (74.2 %)	411 (52.2 %)	<0.001
Antidepressant/neuroleptic, n (%)	0	13 (1.6 %)	0.383
Prebiotic/ probiotic, n (%)	41 (46.1 %)	286 (36.3 %)	0.083
Antisecretory drug (H_2 blocker or proton pump inhibitor)	22 (24.7 %)	156 (19.8 %)	0.268
Other	20 (22.5 %)	199 (25.3 %)	0.608

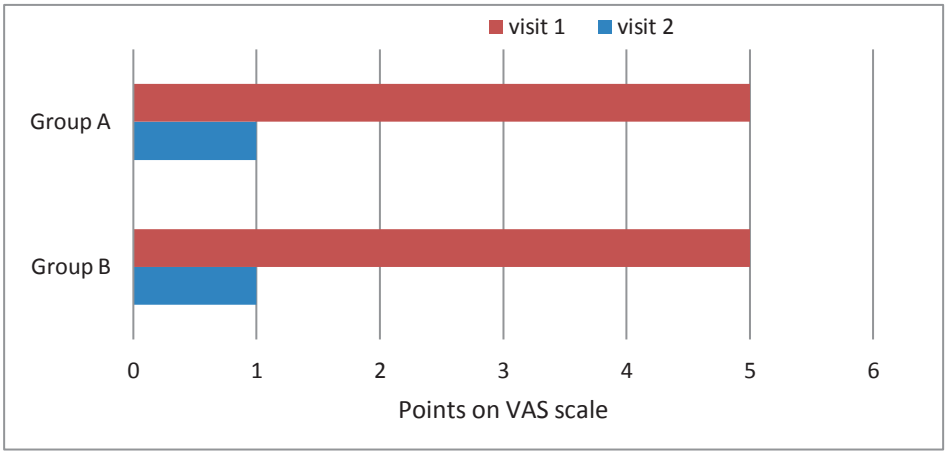

Fig. 3. Mean VAS scores of biliary pain severity over time in groups A and B. A diagram shows mean VAS scores of biliary pain severity at Visit 1 (in red) and Visit 2 (in blue)

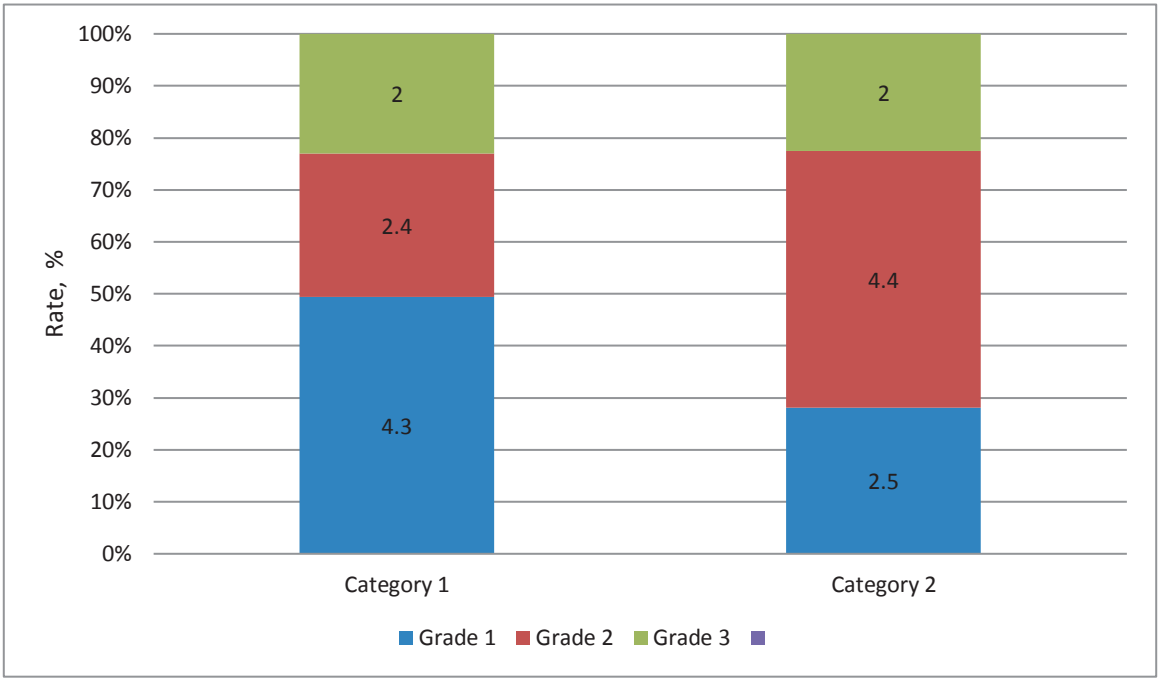

Fig. 4. Distribution of RAPID scores in groups A and B at Visit 1. Diagrams show rates of different biliary pain interference with daily living activities. Grade 1 interference (the lowest, corresponding to a score of 0–5) is blue, grade 2 corresponding to a score of 6–10 is red, grade 3 corresponding to a score of 11–20 is green, and grade 4 (the highest grade, a score of ≥21) is purple

to baseline scores in each group) (Fig. 3). As a result, a significant decrease in a VAS score of pain severity from 5 ± 1 to 1 ± 2 points ($p < 0.001$) was noted in a total group. Analysis of changes in VAS scores was of special importance, while *the primary efficacy criterion* implied assessment of a percentage of patients who achieved a ≥50 % reduction in pain intensity on this scale from baseline. This measure was 51 (77.3 %) in group A and 482 (79.8 %) in group B, $p < 0.05$. In some cases, an increase in a VAS score by 1–2 points was recorded: in 5 (7.6 %) patients in group A and in 11 (1.8 %) patients in group B.

Treatment with hymecromone was associated with a significant reduction in mean severity scores of symptoms evidencing gastrointestinal motility disorders (Fig. 10).

Besides, favourable changes in stool consistency with a reduced relative rate of constipation and diarrhea (Fig. 6, $p < 0.001$ for both groups) were noted. In a total group of patients, an incidence of diarrhea during 21 therapy days was reduced from 35.6 % to 25.6 % and from 28.8 % to 14.4 % for constipation ($p < 0.001$) (Fig. 6).

In a total group, treatment was associated with significant ultrasound changes in gallbladder content (Fig. 8): a significant reduction in the detection rate of biliary sludge and bile heterogeneity. No significant change in the liver echogenicity, vascular markings, parenchyma homogeneity was noted ($p > 0.05$).

48 patients who had ultrasonic cholecystography done at Visits 1 and 2 administered ursodeoxycholic acid as well. Ultrasonic cholecystography findings are shown in Figure 11. Comparing Visit 1 and 2 findings, a total group showed a significant reduction in gallbladder volume under fasting conditions ($p < 0.001$) and in gallbladder emptying (%) 10 minutes after a choleretic breakfast ($p < 0.001$) evidencing a recovery of its motor-evacuation function. No significant between-group differences were found ($p > 0.05$).

The SF-12 scores were analysed at Visits 1 and 2 (Table 2). Treatment was associated with a significant increase in mean scores of physical and mental functioning in both groups ($p < 0.001$, table 2).

However, no clinically significant increase in the SF-12 score of the quality of life (changes by ≥10 points) was noted in any group. Thus, a *secondary efficacy criterion* was established in this study.

Compliance to a 21-day therapy. 679 (77.4 %) patients of a total group reported about drug intake

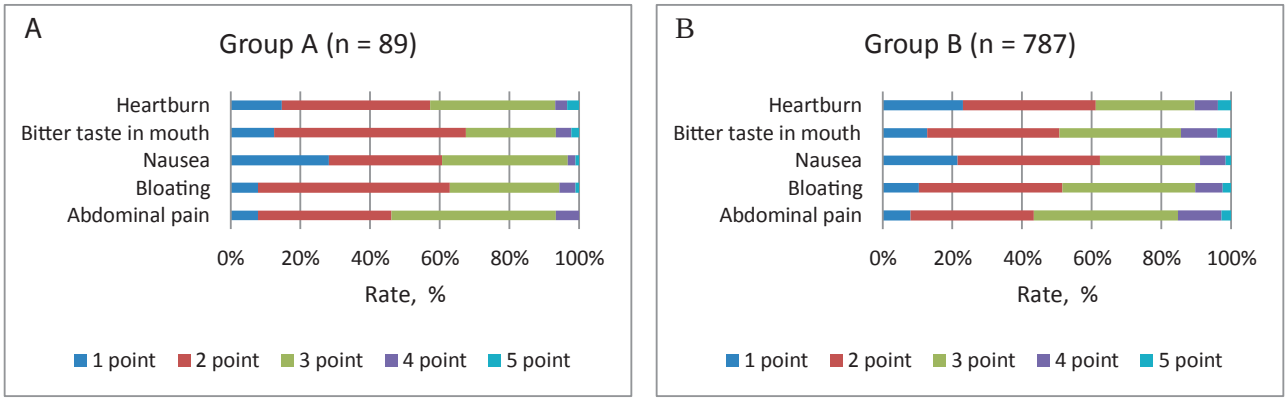

Fig. 5. Distribution of Likert severity scores for dyspeptic signs evidencing upper gastrointestinal motility disorder ("biliary dyspepsia") in groups A and B at Visit 1: A — in group A, B — in group B

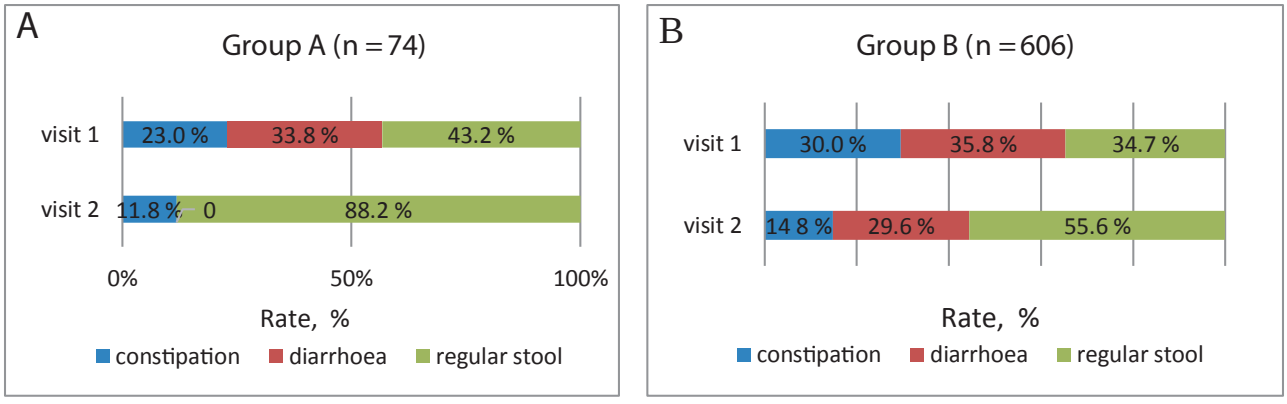

Fig. 6. Changed rates of normal stool, constipation, and diarrhea on treatment with hymecromone in the study groups: A — in group A, B — in group B

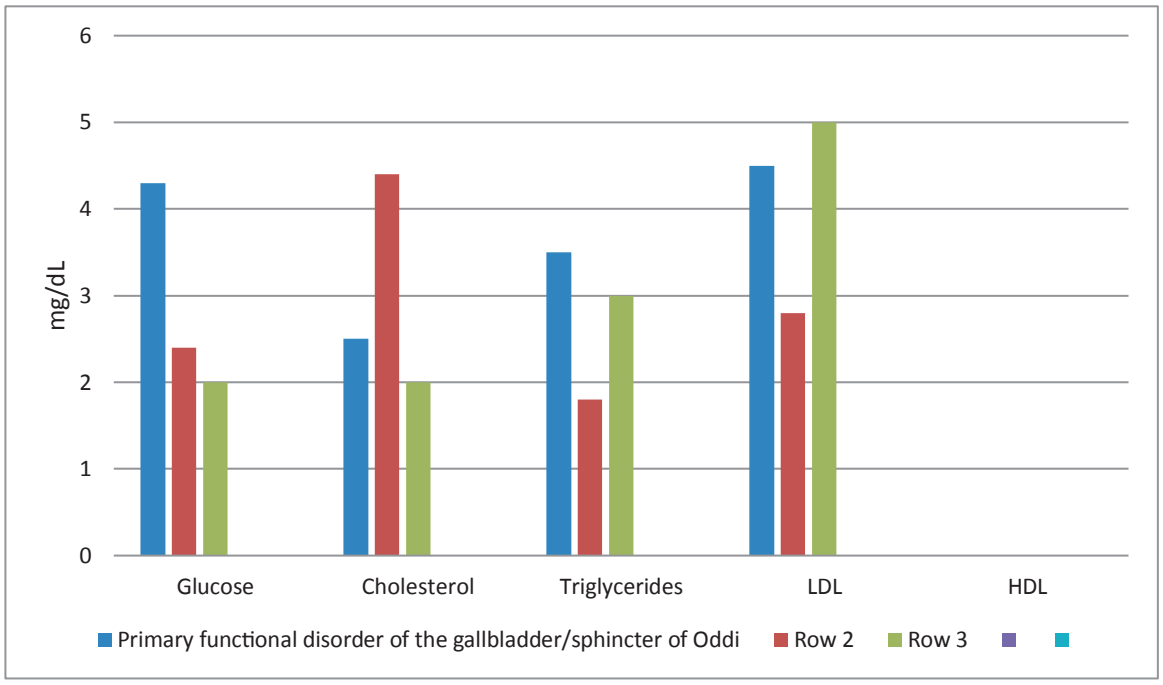

Fig. 7. Glycemic control and serum lipid profile in different bile duct diseases in the total patient group (n = 877)

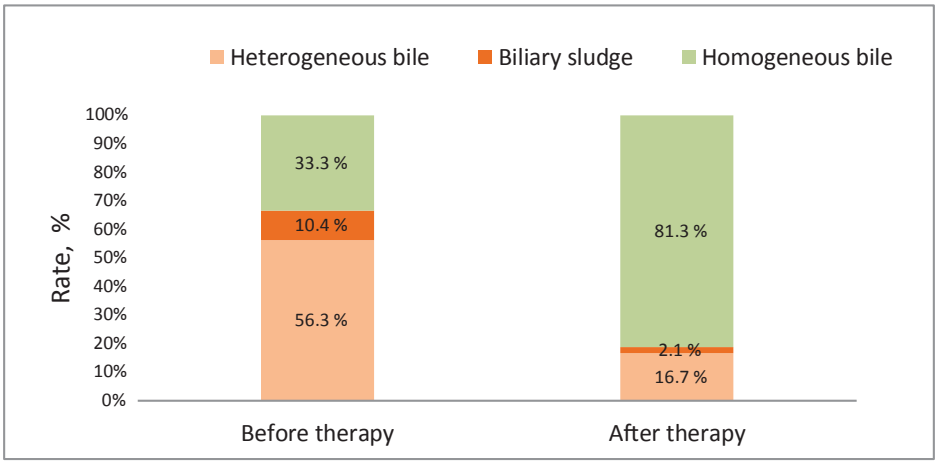

Fig. 8. On-treatment evaluation of bile homogeneity in a total group (n = 48). Detection rates of homogeneous, heterogeneous bile, and distinct biliary sludge were shown

during a 21-day recommended period of time. No significant differences between groups A and B were found (74.2 % versus 77.8 %, p = 0.425). Compliance to a complete therapy course was significantly higher in patients who were previously treated with Odeston: 84.6 % versus 76.1 % (p = 0.026) in a total group, 85.6 % versus 76.3 % (p = 0.025) in group B, and no significant differences were observed in group A.

Patient satisfaction with treatment. Data on evaluation of treatment satisfaction were obtained in 675 (77 %) patients in a total group. A vast majority of patients in a total group and in separate groups A and B evaluated treatment satisfaction as "complete". A number of patients who were completely satisfied with treatment was higher in group B (83.10 % versus 69.70 %, p = 0.027) (Fig. 12).

Figure 13 shows a distribution of scores such as "completely satisfied" and "more likely satisfied" in groups A and B depending on the baseline RAPID score. At Baseline, according to the RAPID scores, a higher rate of moderate interference of pain with daily living activities, in a ratio of about 1.7:1 to group A, was noted in group B (Fig. 4). Assessment of patient satisfaction with treatment outcomes demonstrates a high efficacy of Odeston 1200 mg a day for such patients: a percentage of patients satisfied with treatment was about 2.6 times higher than in group B (p < 0.005).

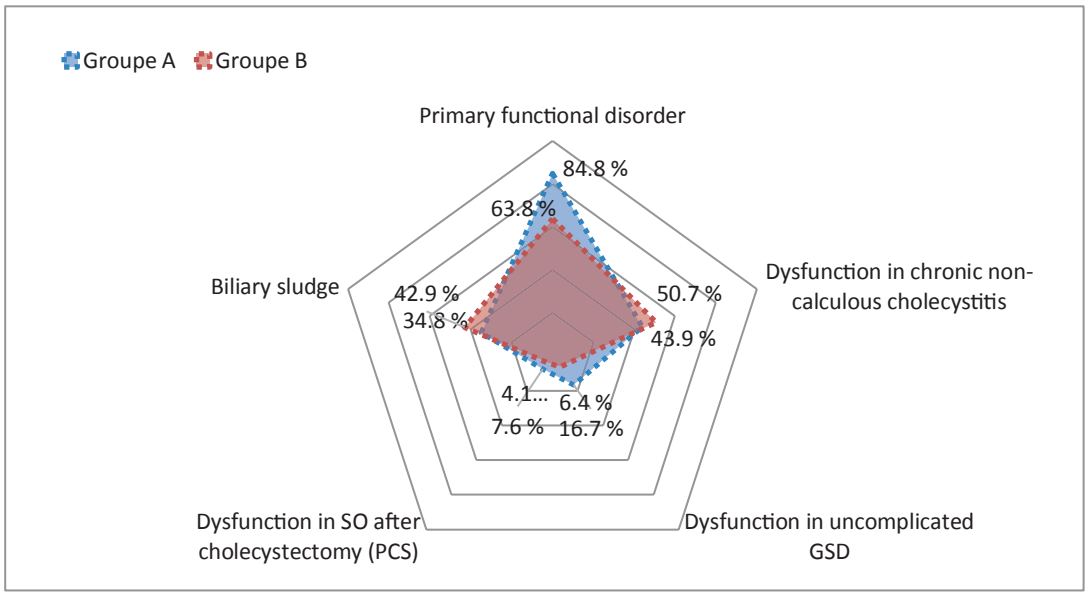

Fig. 9. Nosological structure of groups A and B at Visit 2. A diagram shows a rate of different diseases of the bile ducts in patients. Group A marked by blue, and group B — by red

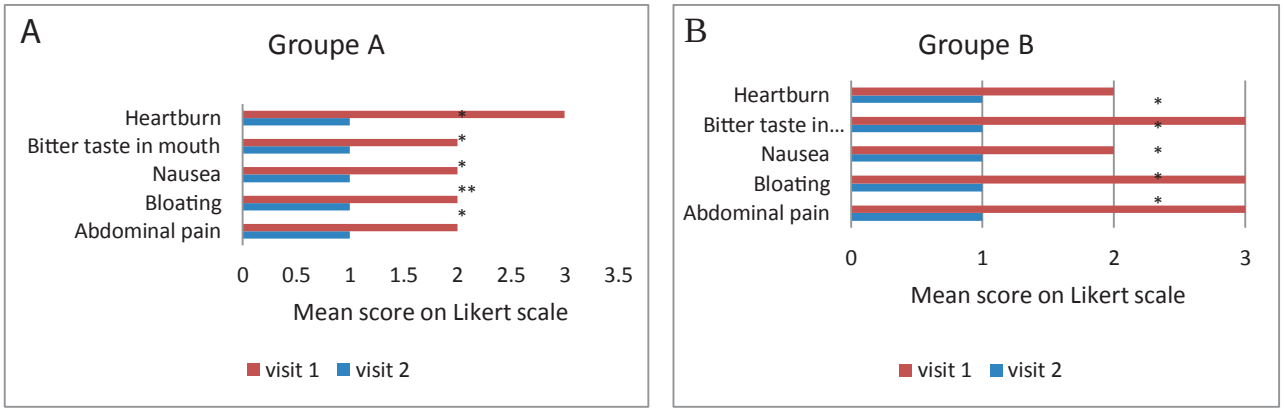

Fig. 10. Changes in mean Likert scale severity scores of symptoms evidencing digestive tract motility disorders in groups A and B on treatment with hymecromone: A — in group A, B — in group B. * $p < 0.01$, ** $p < 0.05$

In both groups, the rate of complete satisfaction with treatment was higher in diagnosis of "biliary tract dysfunction in patients with chronic non-calculous cholecystitis" ($p = 0.034$) and lower in diagnosis of "biliary tract dysfunction in patients with uncomplicated GSD" ($p = 0.029$).

Discussion. Bile duct disease is one of the most common diseases in the physician's routine practice; spasmolytic agents hold the important place in treatment of biliary pain and concurrent dyspeptic symptoms. The benefits of hymecromone (Odeston) are associated with its pharmacokinetic peculiarities with a predominant accumulation in bile and therefore selective action on the smooth muscle cells of the bile ducts.

The primary purpose of the prospective non-interventional observational study conducted was to study an experience of Kazakhstan physicians in administration of hymecromone (Odeston) to substantiate the efficacy of its spasmolytic action in the setting of daily clinical practice. Indications for use of the medicinal product in the study were formulated according to the official product leaflet: primary functional gallbladder or sphincter of Oddi disorder, biliary tract dysfunction in patients with chronic non-calculous cholecystitis, uncomplicated GSD, biliary sludge, sphincter of Oddi dysfunction after a cholecystectomy. It should be noted here that clear diagnostic criteria for chronic cholecystitis were not developed, and the majority of cases in routine practice when patients are diagnosed with "chronic non-calculous cholecystitis" in fact can be attributed to primary functional gallbladder disorder (syn. "acalculous cholecystopathy") [1]. It should also be noted that sphincter of Oddi dysfunction after a cholecystectomy is commonly determined by

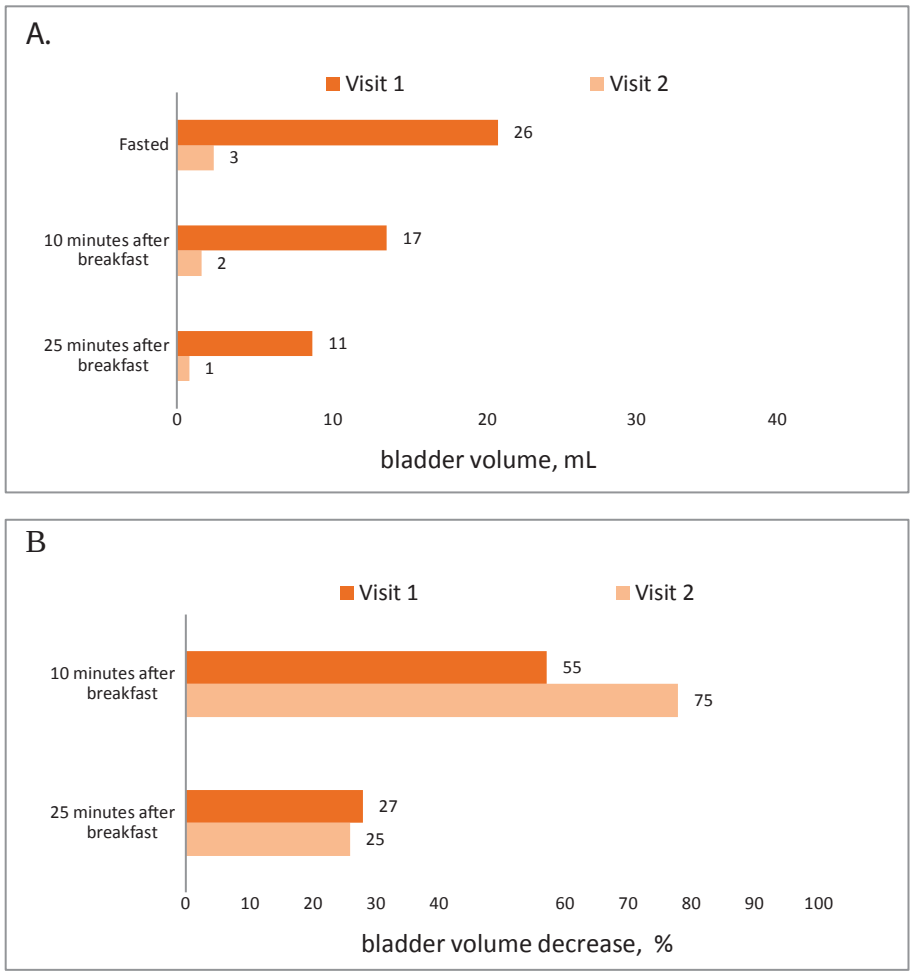

Fig. 11. Changes in cholecystography findings on treatment (A — volume, mL, B — reduction degree, %)

Table 2. The SF-12 scores in groups A and B (total, $n = 636$)

		Visit 1	Visit 2	p
		$M \pm \sigma$	$M \pm \sigma$	
Group A	Physical functioning score	55.98 ± 0.83	56.54 ± 0.46	<0.001
	Mental functioning score	60.39 ± 1.17	60.88 ± 0.86	<0.001
Group B	Physical functioning score	55.57 ± 0.85	56.42 ± 0.48	<0.001
	Mental functioning score	60.37 ± 1.02	60.96 ± 0.85	<0.001

treating physicians with a rather non-specific term "post-cholecystectomy syndrome". One of the tasks of this study was to make the most common "portrait" of a patient to whom physicians prescribe hymecromone — spasmolytic agent selectively acting on the bile ducts.

Patient selection for participation in the study was carried out in the setting of routine clinical practice. The medicinal product was administered when a treating physician considered it appropriate, inclusion criteria completely corresponded to indications for drug administration, and exclusion criteria were maximally close to those settings in which the medicinal product is not administered in real practice. Practicing physicians, who work in settings customary for them and who agreed to take part in this work that minimizes a risk of confounding results, were involved as study doctors in this study.

877 patients were enrolled at Visit 1. Before therapy, biliary pain episodes and different complaints the origin of which could be reasonably explained by upper gastrointestinal (heartburn, bitter taste in mouth, bloating) and intestinal dysfunction (abnormal bowel pattern such as diarrhea or constipation, chronic recurrent abdominal pain of unclear localization) were recorded. Some patients already received therapy with Odeston alone and in combination with ursodeoxycholic acid. Functional disorder,

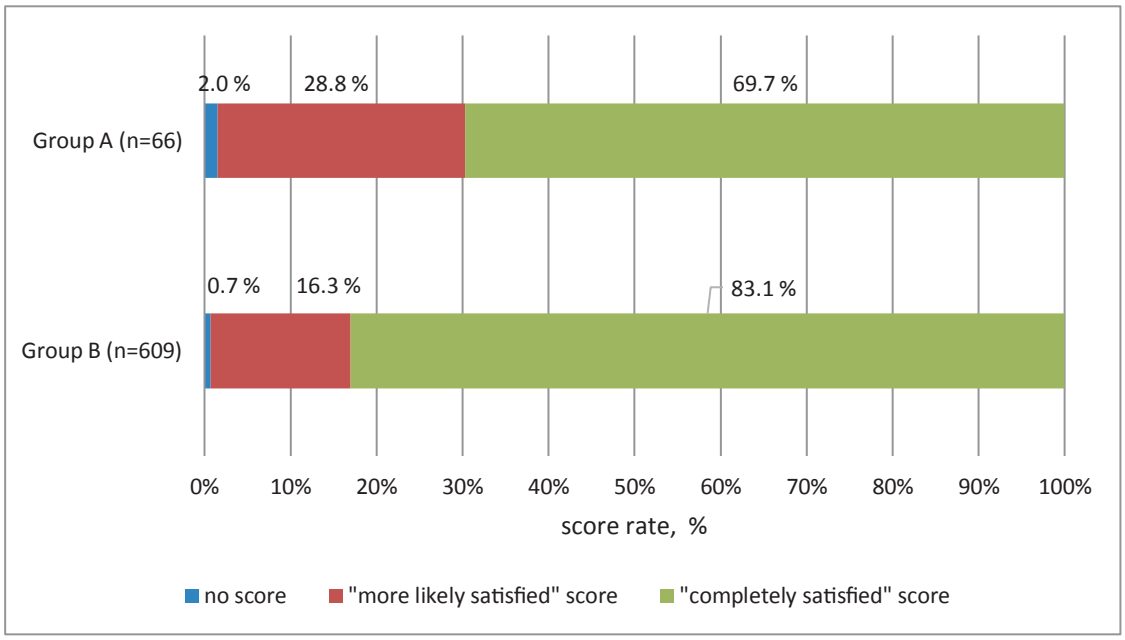

Fig. 12. Patient satisfaction with treatment in percent scores in groups A and B

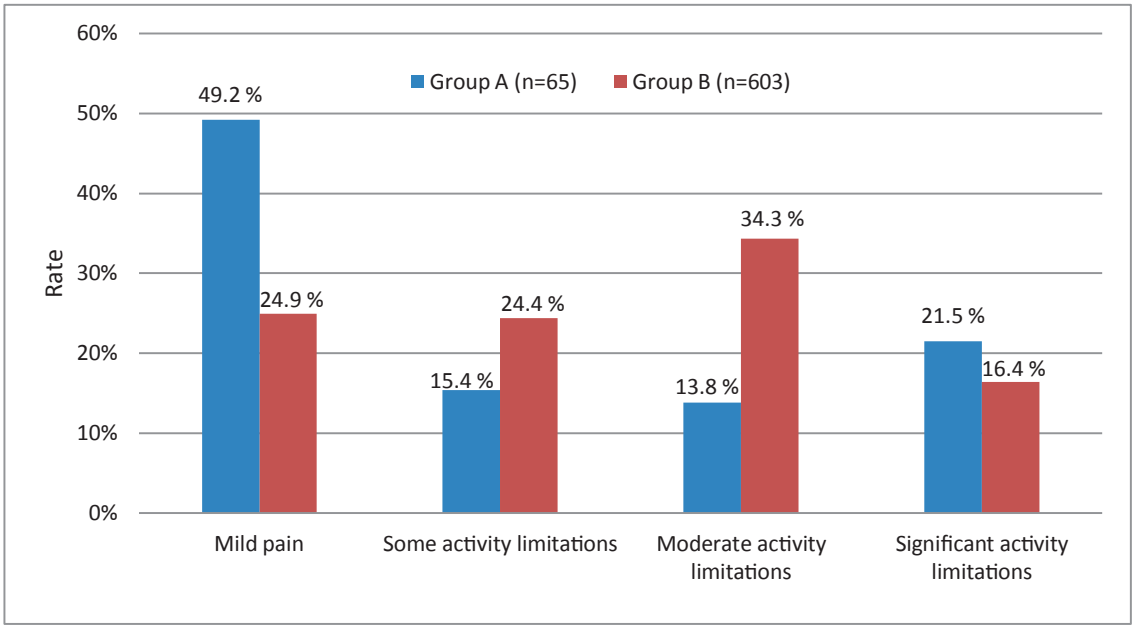

Fig. 13. Distribution of all treatment satisfaction scores, such as “completely satisfied” and “more likely satisfied”, depending on the RAPID scores

uncomplicated GSD, biliary sludge were diagnosed based on clinical data and data from the previous study [19, 20]. The main contribution to a pattern of indications for administration of hymecromone was made by primary functional disorders and biliary dysfunction in chronic non-calculous cholecystitis (as was mentioned, these cases may be consistent with primary functional disorders). In a large part of cases (about 30 %), a combination of diseases/ syndromes reflecting bile duct disease was diagnosed in patients. “Primary functional biliary disorder” with “biliary tract dysfunction due to chronic non-calculous cholecystitis” and “biliary tract dysfunction due to chronic non-calculous cholecystitis” and “biliary sludge” were attributed to the most common combinations. Such combinations are explained not only by a valid combination (e.g., with biliary sludge), but also by a peculiar duplication of diagnoses (e.g., primary functional disorder and dysfunction due to non-calculous cholecystitis). Such peculiarities

reflect the real practice problems where a consistent terminology and consistent views about a clinical picture of different bile duct diseases are not well established.

Most patients were middle-aged. Such characteristics as a sufficiently high frequency of smoking, living alone, predominantly mental work among study participants, generally provide a "portrait" of a contemporary urban dweller who is particularly prone to biliary dysfunction because of his/her lifestyle habits.

Study doctors selected a dose of Odeston at their discretion. Thus, two groups of patients were determined: patients receiving therapy with hymecromone 600 mg a day (n = 89) and patients receiving the medicinal product in a dose of 1200 mg a day (n = 788). It was recommended to all patients to take the medicinal product for 21 days. It should be noted here that Odeston in a daily dose of 600 mg was administered in 10.1 % of cases, and a 1200 mg dose was administered in 89.9 %. Thus, the rate of prescription of hymecromone in a high dose was 9 times higher. It seemed that a selection of one or another dose did not depend on disease type, while no significant differences in indications for Odeston administration were noted between groups A and B. A history of prior therapy with Odeston or ursodeoxycholic acid did not affect a selection of a lower or higher dose of the medicinal product as well. However, considering that the incidence of concomitant therapy with ursodeoxycholic acid was significantly higher in group A than in group B (72.2 % versus 52.2 %) it is suggested that a concomitant administration of ursodeoxycholic acid is the factor that could affect the doctor's decision to prescribe a lower dose of Odeston.

The RAPID score of pain interference with the patient daily living activities appeared to be different with more severe cases being prevalent in group B. Thus, it can be concluded that the rate of administration of Odeston in a lower dose of 600 mg a day was significantly higher in cases with no significant interference of pain with daily living activities. A higher dose of 1200 mg a day was administered in a more significant pain interference. Based on the analysis of treatment satisfaction it can be concluded that Odeston 1200 mg was optimal for treatment of patients with moderate pain interference with daily living activities. A trend towards a higher efficacy of the medicinal product in the absence of gallbladder stones in patients was noted.

The study tasks included also an assessment of on-treatment changes in clinical and ultrasound symptoms, effects on the quality of life, compliance to a 21-day therapy and patient satisfaction with treatment. At baseline, pain severity according to a VAS score was moderate (mean score of 5 points) which can be considered typical for biliary pain caused by spasm without mechanical obstruction. Treatment was associated with a significant reduction in the VAS score of pain severity without significant differences between groups receiving different doses of Odeston.

A pronounced favorable effect of Odeston on other symptoms (dyspepsia, abnormal stool pattern) evidencing digestive tract dysfunction was observed. Such effect can be explained not only by an improved bile outflow in the duodenum, but also by a spasmolytic effect of hymecromone on the proximal small intestine. It is likely that a combination of the spasmolytic and moderate choleretic effects optimizes the initial stages of digestion facilitating resolution of dyspepsia symptoms and stool normalization. Importantly that a percentage of patients with unformed stool in group B, receiving a 1200 mg daily dose, decreased despite a potential risk of diarrhea due to the choleretic action of the medicinal product. It can be assumed that it is connected with a positive effect of the medicinal product on the motility of the first part of the intestine.

Ultrasonographic cholecystography performed in 48 patients showed data evidencing a recovery of the gallbladder motor-evacuation function on treatment with hymecromone. Based on the drug mechanisms of action it can be assumed that such effect is associated with a spasmolytic effect on the bile duct sphincters and removal of "functional obstruction" of the bile outflow.

According to patient survey, a duration of hymecromone administration corresponded to a recommended 21-day duration in 66 (74.2 %) patients in group A and in 613 (77.8 %) patients in group B (non-significant difference, p = 0.425). It can be concluded that though compliance to treatment in both groups did not reach an ideal measure of ≥90 %, as a whole, considering a sufficiently long duration of treatment (21 days), compliance was close to 80 % and was not dose-dependent. The rest of the patients did not adhere to a recommended duration of treatment for different reasons not related to poor drug tolerability.

The patients from both groups demonstrated a high level of satisfaction with treatment with a higher percentage of patients completely satisfied with treatment among those who received hymecromone 1200 g a day and who had a more significant pain interference with daily living activities at baseline.

Thus, the results of the provided observational study allowed to identify some peculiarities of management of patients with biliary dysfunction: necessity to provide doctors with internationally accepted diagnostic terminology as part of clinical guidelines, different level of biliary pain interference with daily living activities — minor to significant, a common combination of biliary pain with symptoms of digestive tract motility disorder (bitter taste in mouth, flatulence, bloating, diarrhea, constipation, etc.), sufficiently high efficacy of hymecromone spasmolytic selectively acting on the bile ducts, high satisfaction with treatment with a dose of 1200 mg a day, particularly in more pronounced pain interference with daily living activities, and also a potential of

retreatment with hymecromone in combination with ursodeoxycholic acid.

Kazakhstan is a large economically developed nation state with medical traditions being closely and historically tied to the Russian ones. A total morbidity pattern of the population is also close to that in the Russian Federation. So a provided experience is certainly useful for doctors of both countries.

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Information about the authors

Alexander V. Nersesov — Dr. Sci. (Med.), Prof., Head of the Chair of Gastroenterology, Asfendiyarov Kazakh National Medical University.
Contact information: alexander.nersesov@gmail.com;
Almaty, Ayteke bi str., 120.
ORCID: https://orcid.org/0000-0002-8601-3966

Dzhamilya A. Kaybullaeva — Cand. Sci. (Med.), Assoc. Prof., Chair of Gastroenterology, Asfendiyarov Kazakh National Medical University.
Contact information: kaibullaev@mail.ru;
Almaty, Tole bi str., 94.
ORCID: https://orcid.org/0000-0002-0783-4441

Venera S. Rakhmetova — Dr. Sci. (Med.), Prof., Chair of Internal Medicine, Astana Medical University.
Contact information: venerarakhmetova@gmail.com;
Nur-Sultan, Beybitshilik str., 49A.
ORCID: https://orcid.org/0000-0001-5721-6409

Irina A. Lozinskaya — Physician (gastroenterology), Head of Pathology Centre, Regional Clinical Hospital.
Contact information: lozinskay@gmail.com;
Karaganda, Erubaevoy str., 15.
ORCID: https://orcid.org/0000 0002 4075 1728

Asem K. Kurmangalieva — Physician (gastroenterology), Regional Clinical Hospital.
Contact information: asemkenesbek@mail.ru;
Chimkent, Mayly Kozha str., 4.
ORCID: https://orcid.org/0000-0003-0658-701X

Venera S. Ayupova — Physician (gastroenterology), City Outpatient Clinic No. 5.
Contact information: Almaty.hep@mail.ru;
Almaty, Makataeva str., 141.
ORCID: https://orcid.org/0000 0001 9861 6273

Aida B. Orazbaeva — Physician (gastroenterology, infectiology), ICLINIC Medical Centre.
Contact information: aida.orazbayeva18@gmail.com;
Nur-Sultan, Mangilik El str., 37.
ORCID: https://orcid.org/0000-0003-0529-1583

Ayzhan K. Kanabaeva — Physician (gastroenterology), "Beta i K" Medical Centre LLP.
Contact information: aizhan.kanabaeva@mail.ru;
Almaty, Koktem 3 mikrorayon, 17.
ORCID: https://orcid.org/0000-0001-8178-182X

Yuliya O. Shulpekova* — Cand. Sci. (Med.), Assoc. Prof., Chair of Internal Disease Propaedeutics, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: shulpekova_yu_o@staff.sechenov.ru;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0002-5563-6634

* Автор, ответственный за переписку / Corresponding author