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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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COMPARATIVE EFFICACY OF PHENOBARBITAL, FLUMECINOL, AND URSODEOXYCHOLIC ACID IN THE MANAGEMENT OF HYPERBILIRUBINEMIA IN PATIENTS WITH GILBERT SYNDROME: A PROSPECTIVE COMPARATIVE STUDY

Rostomova N.E, Asmalova P.A, Khiroev S.I, Dzhanumova K.G, Dzebisova D.A, Bozhik P.E, Kasich S.O, Kungurova D.L, Rasulov M.N, Cherkasova E.I, Kravtsova A.A, Rutvina I.A, Reutov M.O.

NWSMU named after I.I. Mechnikova, Saint-Petersburg, Russia. Federal State Budgetary Institution "V.A. Almazov National Medical Research Center, Chita State Medical Academy.

Abstract.

Background/Aim: Gilbert syndrome (GS) is a common inherited disorder of bilirubin metabolism characterized by unconjugated hyperbilirubinemia due to reduced UGT1A1 activity. Despite the availability of several pharmacological agents capable of modulating bilirubin levels, no controlled comparative studies have systematically evaluated their relative efficacy and tolerability in adult patients with GS. The aim of this study was to compare the efficacy and safety of phenobarbital, flumecinol, and ursodeoxycholic acid (UDCA) in reducing serum bilirubin levels in patients with Gilbert syndrome.

Methods: A prospective, randomized, open-label, parallel-group study was conducted. Sixty patients with confirmed GS and baseline total bilirubin ≥34 μmol/L were randomized 1:1:1 to receive phenobarbital 50 mg/day (Group A, n=20), flumecinol 200 mg/day (Group B, n=20), or UDCA 10 mg/kg/day (Group C, n=20) for 14 days. The primary endpoint was the change in total serum bilirubin (Δ total bilirubin) from baseline to Day 14. Secondary endpoints included changes in unconjugated bilirubin, proportion of patients achieving ≥30% bilirubin reduction, and tolerability parameters. Intergroup comparisons were performed using one-way ANOVA with post hoc Tukey's test.

Results: All three groups demonstrated significant bilirubin reduction after 14 days. Phenobarbital produced the greatest decrease in total bilirubin (−26.9 ± 7.4 μmol/L), followed by flumecinol (−20.7 ± 6.9 μmol/L) and UDCA (−12.1 ± 6.3 μmol/L; $p < 0.001$, ANOVA). Post hoc analysis confirmed significant differences between all pairwise comparisons: phenobarbital vs. flumecinol ($p = 0.02$), phenobarbital vs. UDCA ($p < 0.001$), and flumecinol vs. UDCA ($p = 0.01$). The proportion of patients achieving ≥30% bilirubin reduction was 85%, 65%, and 30% in Groups A, B, and C, respectively. Similar trends were observed for unconjugated bilirubin. Somnolence was reported in 30% of phenobarbital-treated patients compared with 10% for flumecinol and 5% for UDCA. No clinically significant hepatotoxicity was observed.

Conclusions: Phenobarbital demonstrated the highest efficacy in reducing unconjugated hyperbilirubinemia in patients with Gilbert syndrome but was associated with a higher incidence of somnolence. Flumecinol offers a clinically meaningful bilirubin-lowering effect with a more favorable tolerability profile and may serve as a rational alternative. UDCA showed limited efficacy as a primary strategy for bilirubin reduction in GS and appears more appropriate for patients with concomitant biliary pathology.

Key words. Gilbert syndrome, unconjugated hyperbilirubinemia, UGT1A1, phenobarbital, flumecinol, ursodeoxycholic acid, comparative study, standard deviation (SD).

Introduction.

Gilbert syndrome (GS) is a common benign disorder characterized by unconjugated hyperbilirubinemia resulting from reduced activity of the hepatic enzyme uridine diphosphate–glucuronosyltransferase 1A1 (UGT1A1). Clinically significant elevations in serum bilirubin may adversely affect quality of life and frequently lead to excessive diagnostic evaluation and unwarranted therapeutic interventions.

According to international epidemiological data, the prevalence of GS ranges from approximately 2% to 20% across different ethnic populations, with higher rates reported in South Asia and the Middle East and lower rates in East Asia. In European populations, GS is estimated to affect approximately 5–10% of individuals. The prevalence of genetic variants in UGT1A1 associated with the syndrome may reach up to 40%, underscoring the broad genetic basis of unconjugated hyperbilirubinemia [1,2].

In patients with GS, unconjugated bilirubin concentrations may be substantially elevated compared with the general population, particularly in the presence of known triggers such as fasting, physical exertion, or psychological stress. Persistent or recurrent fluctuations in bilirubin levels can negatively influence quality of life. Reported subjective symptoms include fatigue, generalized weakness, and intermittent jaundice, which often prompt specialist consultations and additional diagnostic investigations [3-5].

Despite its high prevalence, diagnostic criteria remain variable, and GS is frequently misinterpreted as underlying liver disease or hemolysis. Such misclassification may result in unnecessary testing and increased patient anxiety. Current clinical guidelines generally recommend conservative management without pharmacological treatment, as GS is considered a benign condition [2, 3].

Nevertheless, several publications have proposed pharmacological correction of hyperbilirubinemia in cases of markedly elevated bilirubin levels or significant impairment of quality of life. Suggested approaches have included phenobarbital therapy, phototherapy, and pharmacologic enzyme induction. In the present study, pharmacological intervention was considered clinically justified for all enrolled patients, given that total serum bilirubin levels consistently exceeded 34 μmol/L at screening and were accompanied by subjectively significant symptoms—including fatigue, generalized weakness, and recurrent jaundice—that substantially impaired daily functioning and quality of life. These features collectively constituted a clinical indication for a therapeutic trial, notwithstanding the generally conservative nature of current guideline recommendations [2,3].

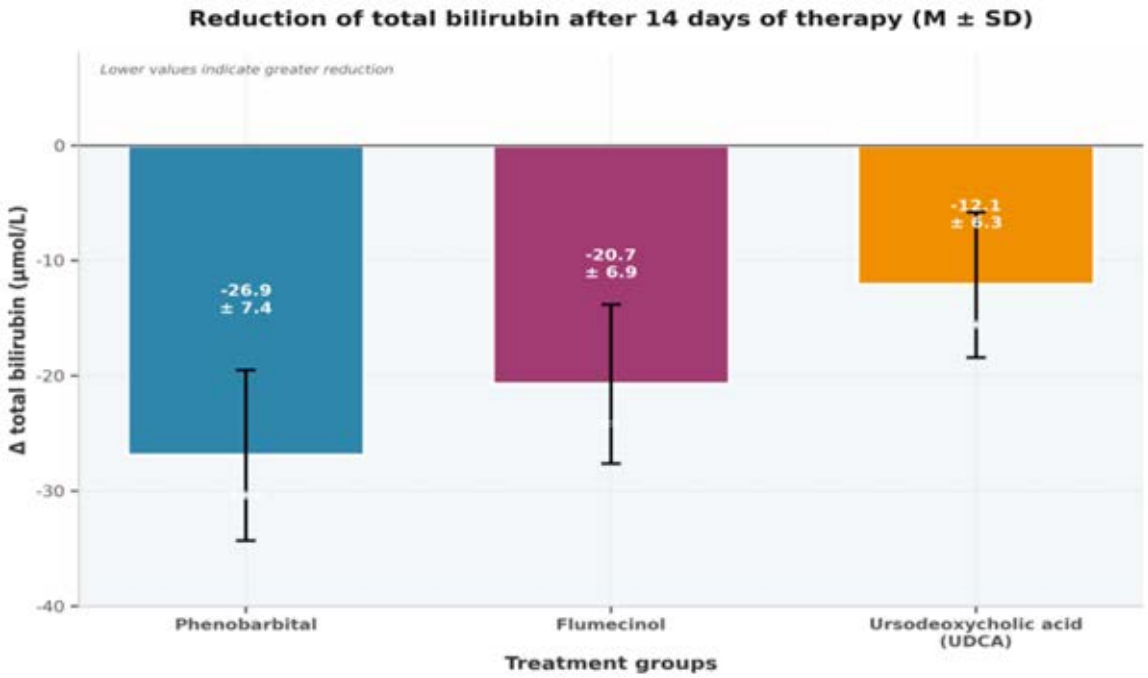

Figure 1. *Intergroup analysis of changes in total serum bilirubin (Δ total bilirubin) using one-way analysis of variance (ANOVA) demonstrated statistically significant differences among the three treatment modalities ($p < 0.001$).*

Table 1. *Changes in Total Serum Bilirubin (μmol/L, Mean ± SD).*

Parameter	Phenobarbital (n=20)	Flumecinol (n=20)	Ursodeoxycholic Acid (n= 20)
Day 0	48,2 ± 7,1	47,6 ± 6,8	46,9 ± 7,5
Day 14	21,3 ± 5,4	26,9 ± 6,2	34,8 ± 7,0
Δ (Reduction)	−26,9 ± 7,4	−20,7 ± 6,9	−12,1 ± 6,3
Proportion of Patients with ≥30% Reduction	85% (17/20)	65% (13/20)	30% (6/20)

Table 2. *Baseline Demographic and Clinical Characteristics of Study Participants.*

Parameter	Phenobarbital (n=20)	Flumecinol (n=20)	UDCA (n=20)
Age, years (Mean ± SD)	27.4 ± 6.2	26.8 ± 5.9	28.1 ± 6.5
Sex, male / female (n)	14 / 6	13 / 7	13 / 7
Baseline total bilirubin, μmol/L (Mean ± SD)	48.2 ± 7.1	47.6 ± 6.8	46.9 ± 7.5
p-value (between groups)	p > 0.2 for all parameters (ANOVA)		

To date, no large-scale controlled trials have systematically compared different pharmacological strategies for reducing serum bilirubin levels in adult patients with GS in terms of efficacy and tolerability. This represents a substantial methodological gap in evidence-based therapeutic decision-making. Moreover, available data regarding such interventions—including comparisons between phenobarbital and alternative agents such as flumecinol or ursodeoxycholic acid—remain limited, fragmented, and largely derived from small, open-label, or non-randomized observational studies.

Materials and Methods.

This study was conducted using a prospective, randomized, comparative, open-label, parallel-group design with a 1:1:1 allocation ratio. The open-label design was adopted for practical and pharmacological reasons; however, it may have introduced reporting bias in the assessment of subjective outcomes, particularly somnolence, given the known sedative properties of phenobarbital. This limitation is discussed in the Limitations section. The duration of follow-up and pharmacological intervention was 14 days. A total of 60 patients with clinically and laboratory-confirmed Gilbert syndrome were enrolled and assigned by simple randomization to three equal groups (n = 20 per group).

The study was approved by the Local Ethics Committee of NWSMU named after I.I. Mechnikov (Protocol No. 9, dated February 5, 2026). All participants provided written informed consent prior to enrollment in accordance with the Declaration of Helsinki and applicable national regulatory requirements.

Inclusion criteria were as follows: age 18–45 years; persistent unconjugated hyperbilirubinemia with a total serum bilirubin level ≥34 μmol/L at screening; and exclusion of alternative causes of hyperbilirubinemia, including hemolytic disorders and viral hepatitis.

To ensure sample homogeneity, patients were excluded if they had aminotransferase levels exceeding twice the upper limit of normal, or had used medications known to induce or inhibit hepatic microsomal enzymes within 4 weeks prior to enrollment. An additional exclusion criterion was the presence of factors

capable of acutely influencing bilirubin levels, particularly fasting episodes within 72 hours before baseline assessment.

Interventions:

Patients received one of the following pharmacological regimens:

- **Group A:** phenobarbital 50 mg once daily at bedtime;
- **Group B:** flumecinol 200 mg daily;
- **Group C:** ursodeoxycholic acid 10 mg/kg/day.

All medications were administered for 14 consecutive days without dose adjustment. The selected dosages were based on previously published data: phenobarbital at 50 mg/day is the standard low-dose enzyme-inducing regimen reported in the literature for reduction of unconjugated bilirubin in adults [4,6]; flumecinol at 200 mg/day corresponds to the dose used in prior small-scale open-label investigations of hepatic enzyme induction; ursodeoxycholic acid at 10 mg/kg/day represents the standard hepatoprotective dose established in guidelines for biliary disorders [3]. The 14-day treatment period was selected as sufficient to achieve measurable induction of UGT1A1 activity while minimizing cumulative adverse effects, consistent with pharmacokinetic data from previous studies.

Endpoints:

The primary endpoint was the change in total serum bilirubin (Δ total bilirubin) from baseline (Day 0) to the end of therapy (Day 14).

Secondary endpoints included:

- change in unconjugated bilirubin concentration;
- proportion of patients achieving ≥30% reduction in total bilirubin from baseline;
- tolerability and safety parameters, including subjective somnolence assessment, recording of adverse events, and changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Statistical Analysis:

Statistical analysis was performed using one-way analysis of variance (ANOVA) to assess intergroup differences in Δ total bilirubin. When statistically significant differences were identified, post hoc comparisons were conducted using Tukey's test.

A two-sided p value <0.05 was considered statistically significant. Results are presented as mean ± standard deviation (M ± SD).

Baseline Characteristics and Treatment Outcomes:

At enrollment, the study groups did not differ significantly with respect to key demographic or clinical–laboratory parameters. Mean age, sex distribution, and baseline total bilirubin levels were comparable across the three groups, with no statistically significant intergroup differences ($p > 0.2$ for all comparisons). These findings support the adequacy of the randomization process and permit attribution of observed differences to the administered interventions rather than to baseline imbalances.

After completion of the 14-day treatment course, all groups demonstrated a statistically significant reduction in total serum bilirubin compared with baseline values. However, the magnitude of the effect varied substantially according to the pharmacological regimen.

The most pronounced decrease in total bilirubin was observed in the phenobarbital group (−26.9 ± 7.4 μmol/L). In the flumecinol group, the reduction was moderate (−20.7 ± 6.9 μmol/L), whereas the smallest decrease was recorded in the ursodeoxycholic acid group (−12.1 ± 6.3 μmol/L). Intergroup comparison using one-way ANOVA revealed statistically significant differences among the three treatment strategies ($p < 0.001$). Post hoc analysis (Tukey test) demonstrated that bilirubin reduction in the phenobarbital group was significantly greater than in the flumecinol group ($p = 0.02$) and the ursodeoxycholic acid group ($p < 0.001$). In turn, flumecinol was significantly more effective than ursodeoxycholic acid ($p = 0.01$).

Similar trends were observed in the analysis of unconjugated bilirubin, supporting a pathogenetically targeted effect of bilirubin glucuronidation inducers. The proportion of patients achieving a clinically meaningful reduction in total bilirubin (≥30% from baseline) was 85% in the phenobarbital group, 65% in the flumecinol group, and 30% in the ursodeoxycholic acid group.

Regarding tolerability, the most frequent adverse event in the phenobarbital group was somnolence (30% of patients). This effect was reported in 10% of patients receiving flumecinol and 5% of those treated with ursodeoxycholic acid. No clinically significant changes in aminotransferase activity were detected during the study period.

Overall, the findings indicate a statistically significant superiority of phenobarbital in reducing hyperbilirubinemia in patients with Gilbert syndrome. Flumecinol demonstrated a more favorable tolerability profile with moderately lower efficacy, whereas ursodeoxycholic acid exerted the least pronounced effect on unconjugated bilirubin levels within the context of short-term therapy.

Intergroup Comparisons and Additional Results: Intergroup analysis of changes in total serum bilirubin (Δ total bilirubin) using one-way analysis of variance (ANOVA) demonstrated statistically significant differences among the three treatment modalities ($p < 0.001$). Post hoc analysis with Tukey's test revealed that phenobarbital therapy resulted in a significantly greater reduction in bilirubin levels compared with flumecinol ($p = 0.02$) and ursodeoxycholic acid ($p < 0.001$). In turn, flumecinol showed significantly higher efficacy than ursodeoxycholic acid ($p = 0.01$).

Analysis of unconjugated bilirubin dynamics confirmed these findings. The most pronounced decrease in unconjugated bilirubin concentration was observed in the phenobarbital group (−23.1 ± 6.5 μmol/L), followed by the flumecinol group (−17.4 ± 6.1 μmol/L), whereas the smallest reduction was recorded in the ursodeoxycholic acid group (−9.2 ± 5.8 μmol/L). Intergroup differences for this parameter were also statistically significant ($p < 0.001$).

Tolerability and Safety: Assessment of tolerability revealed differences in the frequency of subjective adverse events among treatment groups. Somnolence, an expected pharmacodynamic effect of phenobarbital, was reported in 30% of patients (6/20) receiving this agent. In comparison, somnolence occurred in 10% of patients (2/20) in the flumecinol group and 5% (1/20) in the ursodeoxycholic acid group. No severe adverse events requiring treatment discontinuation were recorded.

Serial biochemical monitoring demonstrated no clinically significant increases in aminotransferase activity (ALT, AST) in any group during the study period, indicating an acceptable short-term safety profile for the investigated regimens [7-9].

Discussion.

The present findings support the pathogenetic rationale for pharmacological induction of bilirubin glucuronidation in patients with Gilbert syndrome. Phenobarbital achieved the most substantial reduction in both total and unconjugated bilirubin levels, consistent with its known enzyme-inducing effects on hepatic microsomal systems, including UGT1A1 [6,8,10-12]. However, the higher incidence of somnolence in the phenobarbital group may limit its clinical applicability, particularly in patients for whom sedative effects or reduced psychomotor performance are undesirable.

Flumecinol demonstrated intermediate efficacy with a more favourable tolerability profile. These results suggest that flumecinol may represent a rational alternative to barbiturates in patients with contraindications to phenobarbital or poor tolerance to sedative effects [7]. The data indicate potential clinical utility of flumecinol as a compromise between efficacy and safety.

Ursodeoxycholic acid exhibited the least pronounced effect on unconjugated bilirubin levels, which is consistent with the absence of a direct pathogenetic mechanism influencing bilirubin glucuronidation. Accordingly, its use appears more appropriate in the context of concomitant biliary pathology (e.g., biliary sludge or cholestasis) rather than as a primary therapeutic strategy for correction of unconjugated hyperbilirubinemia in Gilbert syndrome [11].

Key limitations of this model study include the short duration of follow-up, absence of a placebo-controlled arm, and incomplete control of dietary and behavioural factors potentially affecting bilirubin levels (e.g., caloric intake, physical overexertion, psychological stress). Additionally, the open-label design of the study represents an important methodological limitation: given that phenobarbital is well known for its sedative properties, patients who were aware of their assigned treatment may have differentially over-reported or under-reported somnolence compared with those receiving other agents. This represents a potential source of reporting bias in the assessment of this subjective secondary endpoint. Future studies should consider blinded or double-dummy designs to mitigate this risk. These factors should be considered when interpreting the findings and in the design of future, larger-scale, methodologically rigorous clinical trials.

Conclusion.

Phenobarbital therapy in patients with Gilbert syndrome is associated with the most pronounced reduction in total and unconjugated bilirubin compared with alternative pharmacological strategies, reflecting the greatest effect size. However, its use is accompanied by a higher frequency of sedative adverse events, particularly somnolence, which may limit clinical applicability in certain patient populations.

Flumecinol provides clinically meaningful reduction of hyperbilirubinemia with a more favourable tolerability profile relative to phenobarbital. Considering the balance between efficacy and safety, flumecinol may be regarded as a rational alternative to barbiturates in patients with contraindications or intolerance to sedative effects.

Ursodeoxycholic acid exerts only a modest influence on unconjugated hyperbilirubinemia and does not represent an optimal pathogenetically targeted therapy for Gilbert syndrome. Its clinical use appears more justified in the presence of concomitant biliary dysfunction or cholestatic components rather than as a primary strategy for bilirubin reduction in this population.

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