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# Gastroduodenal effects of leflunomide under experimental adjuvant-induced rheumatoid arthritis and comorbid arterial hypertension

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*Key words: leflunomide, gastroduodenal toxicity, rheumatoid arthritis, arterial hypertension, comorbid pathology*

The poor knowledge of modern medicine regarding the etiological factors and pathogenic mechanisms of the rheumatoid arthritis (RA) in one hand, as well as the lack of efficacy and safety of therapeutic agents and the complexity of their choice on the other hand, have raised challenges in pharmacological treatment of the disease [1–4].

Currently, disease-modifying agents including gold preparations, cytostatics, antibacterial, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and biologics are used for the pharmacological management of RA [5–7]. However, the severe drug side effects, intolerance and insufficient efficacy, as well as the unknown mechanisms involved in rheumatic processes, led to introduce a new class of biologics to the medical practice. Applying genetically engineered immunosuppressors (1990s) and leflunomide (LEF), a synthetic immunosuppressor (1998) for the treatment of RA, created an innovation in the management of the disease [8–10]. Despite the widely and successfully use of the LEF for RA, its pharmacological properties and side effects are not well understood. However, scientific research and clinical data have evidenced some toxic effects of the drug [3, 11].

Immunosuppressants may cause cardiotoxic effects, arterial hypertension (AH), blood pressure destabilization, heart failure, and heart rhythm disorders, etc. For instance, LEF-induced ischemic attack in patients with RA, gastrointestinal toxicity, and hepatotoxicity (development of diarrhea and nausea in 10–15% of patients taking the LEF) have been revealed. Moreover, loading dose of the drug may increase the level of the liver enzymes [12–14]. Additionally, the potential of "unexplained" bleeding, thrombocytopenia, leukopenia, anemia, hypercholesterolemia, vomiting and lethargy has been reported *in vivo* [15], which were caused by LEF.

Since comorbidities, particularly, cardiovascular, gastrointestinal, and oncological diseases, have increased the mortality rate in RA, the safety of immunosuppressants, considering the associated pathologies is an important issue [16–18]. Observation of the potential adverse effects of synthetic immunosuppressants on cardiovascular and gastrointestinal system is necessary. Regarding the cardiac safety of the LEF, investigation of the experimental RA and comorbid hypertension has revealed a need for monitoring the arterial blood pressure and heart rate either when the drug is used alone or in combination with antihypertensive agents [19]. The results of the numerous studies worldwide have confirmed the

importance of monitoring the potential pathological processes of gastrointestinal tract comorbidity, when administering prolonged enteral various pharmacotherapies [20–22].

Notably, the frequency and intensity of drug side effects are points of concern. Particular attention should be paid to the gastroduodenal effects of the drugs during prolonged use in comorbid pathological conditions. This is not only due to the fact that numerous immunosuppressants have gastrointestinal effects, but also, their potential ability to impair the gastrointestinal tract function in comorbid condition, during exercise, anxiety, and depressive disorders [23–26]. However, an unmet clinical need exists.

*The aim of the study* was to examine the gastroduodenal effects of prolonged enteral use of the LEF in rats with adjuvant-induced arthritis (AA) and comorbid AH.

**Materials and methods.** The experiments were conducted on mature male and female nonlinear rats weighing (201.56 ± 2.42) g. Animals were kept under a standard diet in the vivarium with free access to food and water at 20–22 °C and relative humidity of 40–60%. All experiments were performed according to the requirements of the European convention for the protection of vertebrate animals used for experimental and other scientific purposes [27].

Experimental animals were initially acclimatized for 14 days. Afterward, rats were randomly divided into five groups. Animals of control group (10 rats) were treated with 1% starch suspension (0.2 ml) into the stomach through a special metal probe daily from the beginning of the experiment.

Animals of the second group (n = 15) were injected with Complete Freund's adjuvant (CFA) to model AA [28].

Among the salt loading-induced hypertension rats (21 days salt drinking – 1% sodium chloride solution), animals with elevated mean arterial blood pressure higher than 8% of the initial level [(92.5 ± 3.4) mmHg] were selected. Arterial blood pressure in rats was measured and recorded using the Ugo Basele (Italy) sphygmomanometer apparatus [29].

The third group consisted of 15 male and female hypertensive rats, which received CFA, to form a comorbid condition (AH + AA) [30].

The fourth group included 15 AA rats, whose treatment with the LEF (Lefno, Kusum Pharma, India) was started seven days after the CFA administration.

The fifth group consisted of 15 rats with comorbid condition (AH + AA) which were administered the LEF daily, seven days after induction of the inflammatory process. Animals in the third and fifth groups were continued to receive the salt load throughout the study, as described above [30].

1% starch-LEF suspension was administered into the stomach through a special metal probe once daily, in the specific daytime in the following manner: 15 mg/kg rat body weight (rbw) (shock dose) for the first three days, followed by 1.5 mg/kg rbw (therapeutic dose) for 53 days. The doses of the drug were determined based on the species sensitivity. The duration of the drug administration was determined considering the duration of the AA phases, taking into account the fact that the pharmacological effects of the drug are noticed within 2–4 weeks, whereas, the significant effects arise within 6–8 weeks.

The total duration of observation of animals was 81 days including the modeling of AH (21 days), following 60 days after the introduction of CFA to

reproduce the main phases of AA (acute period, period of generalization and disappearance of the inflammatory process) against the background of AH. The administration of the LEF was started 7 days after the introduction of CFA, and continued for 53 days.

In order to determine the gastroduodenal toxic effects of the LEF, rats were anesthetized (60 days after the administration of CFA) and euthanized via cervical dislocation. For further macroscopic examination, the stomach with the upper small intestine (up to 5 cm long) was removed from each animal by laparotomy, and washed out with saline. The stomach was cut off from the intestine with a scissor, and incised along the lesser curvature content of the stomach was emptied, and empty stomach was rinsed with saline. A longitudinal section of the small intestine was prepared. Morphological specimens were fixed with needles on a cortical plate, and the condition of the gastric and upper small intestine (duodenal) mucosa was examined with a binocular magnifying glass. Different types of mucosal lesions (hyperemia, edema, petechiae, and ulcer), degree of the lesions, which were defined as "points", and the intensity of gastroduodenopathy [31] along with the number of animals with the corresponding changes were determined.

**Results and discussion.** Significant lesions of the gastric mucosa were characterized by hyperemia, edema, erosion, and ulceration in AA animals (Table 1). Additionally, punctate hemorrhages and small ulcers were observed in two of the fifteen animals of this group. Hyperemia, mucosal edema and petechial lesions of the esophagus were observed in animals with combined pathology (AH + AA). Duodenal mucosal hyperemia and edema without any ulcerative changes of the duodenum were observed in both pathological conditions. Moreover, occurrence of gastric mucosal lesion was more frequent in both AA and AH + AA groups. The LEF led to an increase in the frequency of rates with certain types of damages to the gastroduodenal mucosa in AA and AH + AA groups. Moreover, the administration of the LEF to the both groups with pathological conditions caused petechiae and ulcers of duodenal mucosa, which were not observed in untreated groups (see Table 1).

Frequency of rats with edema of duodenal mucosa was not changed under the effect of the LEF in AA group. However, this indicator was (significantly) enhanced twice in AH + AA treated animals (from 3 rats in AH + AA jumped to 6 in AH + AA treated).

The prevalence of duodenopathy in rats in the AH+AA group was less than in AA.

In order to determine the degree of the mucosal pathologies, the intensity of gastric and duodenal mucosal lesions (IG and ID, respectively) was measured [31] (Table 2). It was found that the IG point was approximately equal in AA and comorbid pathology group. While, it was higher than the ID point in both groups. The ID in AA (ID = 0.9) was 2.25 times higher than at comorbid condition (ID = 0.4). The LEF enhanced the IG point in AA group (from 1.5 to 3.3), and ID point from 0.9 to 2.0. Additionally, under the effect of the LEF IG and ID points in AH + AA group were enhanced (from 1.5 to 3.0 and 0.4 to 1.4 respectively).

The intensity of damages to the gastric and duodenal mucosa under the effect of the LEF resulted in high levels of gastroduodenal toxicity, which are mentioned in Table 2.

The results of the study proved the gastroduodenal toxic properties of the

Table 1

***The ratio* of the number of animals with the gastroduodenal lesions in different pathological conditions to the total number of the animals in each group 60 days after arthritis induction***

| Pathological indicators | Gastric mucosal lesion | Duodenal mucosal lesion |
|---|---|---|
| *Control* | | |
| Hyperemia | 0/10 | 0/15 |
| Petechiae | 0/10 | 2/15 |
| Edema | 0/10 | 0/15 |
| Ulcers | 0/10 | 0/15 |
| *AA* | | |
| Hyperemia | 11/15 | 8/15 |
| Petechiae | 3/15 | 0/15 |
| Edema | 8/15 | 5/15 |
| Ulcers | 2/15 | 0/15 |
| *AH + AA* | | |
| Hyperemia | 10/15 | 3/15 |
| Petechiae | 5/15 | 0/15 |
| Edema | 8/15 | 3/15 |
| Ulcers | 0/15 | 0/15 |
| *AA + leflunomide* | | |
| Hyperemia | 10/15 | 9/15 |
| Petechiae | 10/15 | 3/15 |
| Edema | 9/15 | 5/15 |
| Ulcers | 7/15 | 2/15 |
| *AH + AA + leflunomide* | | |
| Hyperemia | 11/15 | 4/15 |
| Petechiae | 10/15 | 5/15 |
| Edema | 11/15 | 6/15 |
| Ulcers | 5/15 | 4/15 |

*Note. AA: adjuvant arthritis; AH: arterial hypertension; *the ratio of the number of animals with this effect to the number of animals in the group.*

LEF in experimental RA and comorbid arterial hypertension.

The anti-inflammatory and immunomodulatory effects of the LEF are mainly achieved by its active metabolite A77-1726 (teriflunomide), which inhibits the mitochondrial enzyme dihydroorotate dehydrogenase. Suppression of this enzyme reduces the synthesis of the ribonucleotide uridine monophosphate pyrimidine, leading to a significant limitation of the proliferation of activated and autoimmune lymphocytes. Potential hepatotoxic property of the LEF and its metabolite may be due to the induction of hepatic transaminases, associated with CYP2C9 polymorphism. Moreover, gastroduodenal side effects of the drug may be related to induction of COX-2 and inducible nitric acid. Acidic agents may cause irritation of gastroduodenal mucosa and lesion. However, the exact mechanisms of gastroduodenal toxic

Table 2

*The intensity of gastroduodenal toxic effect of leflunomide in rats (n = 15) in adjuvant-induced arthritis and comorbid hypertension*

| Experimental group | IG points | ID points | Gastric toxicity, % | Duodenal toxicity, % |
|---|---|---|---|---|
| AA | 1.5 | 0.9 | – | – |
| AH + AA | 1.54 | 0.4 | – | – |
| AA + Leflunomide | 3.3* | 2.0 | 54 | 55 |
| AH + AA + Leflunomide | 3.0* | 1.4 | 49 | 71 |

*Note. *p ≤ 0.05 relative value in animals of the intact group.*

effects of the LEF in comorbid pathology need more investigations.

Degeneration of the gastric mucosa with the LEF in AA and hypertension comorbidity increases a need for adjuvant therapy to prevent drug gastroduodenal adverse effects. Also, research in pharmacological area to introduce appropriate drugs is recommended. Furthermore, conducting preclinical and clinical studies to understand the pharmacokinetics, mechanisms of action, and interaction of the LEF in particular, with antihypertensive and gastroprotective agents seems necessary. monitoring cardiovascular and gastrointestinal function, as well as controlling the pain and inflammatory reactions when administering the LEF are the points of concern. Implementation of the results of the study in healthcare practice will help to optimize the treatment regimen for RA and related pathologies.

## Conclusion

Prolonged administration of LEF to rats with adjuvant arthritis and comorbid AH leads to an increase in the frequency of gastroduodenal mucosal pathology and intensity of various types of damages (petechiae, edema, ulcers).

The LEF leads to high levels of gastroduodenal toxicity in rats with AA and combined pathological condition.

The LEF induced higher prevalence of duodenal toxicity than gastric in rats with both AA and hypertension comorbidity.


1. American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. J. A. Singh, K. G. Saag, S. L. Jr. Bridges et al. *Arthritis & rheumatology (Hoboken, N. J.)*. 2016. V. 68 (1). P. 1–26. https://doi.org/10.1002/art.39480.
2. Strategies toward rheumatoid arthritis therapy; the old and the new. M. Abbasi, M. J. Mousavi, S. Jamalzehi et al. *J. Cell Physiol*. 2019. V. 234 (7). P. 10018–10031. https://doi.org/10.1002/jcp.27860.
3. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. J. S. Smolen, R. B. M. Landewé, S. A. Bergstra et al. *Annals of the rheumatic diseases*. 2020. V. 79 (6). P. 685–699. https://doi.org/10.1136/annrheumdis-2019-216655.
4. American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. L. Fraenkel, J. M. Bathon, B. R. England et al. *Arthritis care & research*. 2021. V. 73 (7). P. 924–939. https://doi.org/10.1002/acr.24596.
5. Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. A. Kerschbaumer, A. Sepriano, S. A. Bergstra et al. *Annals of the rheumatic diseases*. 2023. V. 82 (1). P. 95–106. https://doi.org/10.1136/ard-2022-223365.
6. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. A. Sepriano, A. Kerschbaumer, S. A. Bergstra et al. *Annals of the rheumatic diseases*. 2023. V. 82 (1). P. 107–118. https://doi.org/10.1136/ard-2022-223357.

7. American College of Rheumatology/EULAR remission criteria for rheumatoid arthritis: 2022 revision. P. Studenic, D. Aletaha, M. de Wit et al. *Annals of the rheumatic diseases*. 2023. V. 82 (1). P. 74–80. https://doi.org/10.1136/ard-2022-223413.
8. Breedveld F. C., Dayer J. M. Leflunomide: mode of action in the treatment of rheumatoid arthritis. *Annals of the rheumatic diseases*. 2000. V. 59 (11). P. 841–849. https://doi.org/10.1136/ard.59.11.841.
9. Cohen S. B., Iqbal I. Leflunomide. *International Journal of Clinical Practice*. 2003. V. 57 (2). P. 115–120.
10. Efficacy and tolerability of leflunomide in difficult-to-treat polymyalgia rheumatica and giant cell arteritis: a case series. T. Adizie, D. Christidis, C. Dharmapaliah et al. *International Journal of Clinical Practice*. 2012. V. 66 (9). P. 906-909. https://doi.org/10.1111/j.1742-1241.2012.02981.x.
11. Leflunomide use and risk of lung disease in rheumatoid arthritis: a systematic literature review and metaanalysis of randomized controlled trials. R. Conway, C. Low, R. J. Coughlan et al. *The Journal of Rheumatology*. V. 43 (5). P. 855–860. https://doi.org/10.3899/jrheum.150674.
12. Navarro C. E., Enríquez-Ruano P., Enríquez-Ruano M. N. Leflunomide-induced recurrent-transient ischaemic attacks in a patient with rheumatoid arthritis: first case report. *European Journal of Clinical Pharmacology*. 2020. V. 76 (9). P. 1341–1342. https://doi.org/10.1007/s00228-020-02907-y.
13. A retrospective study on the safety and efficacy of leflunomide in dogs. M. Sato, J. K. Veir, M. Legare, M. R. Lappin. *Journal of Veterinary Internal Medicine*. 2017. V. 31 (5). P. 1502–1507. https://doi.org/10.1111/jvim.14810.
14. Robert I. Fox, Simon M. Helfgott. Pharmacology, dosing, and adverse effects of leflunomide in the treatment of rheumatoid arthritis. 2024. URL: https://medilib.ir/uptodate/show/7515.
15. Walton S. A., Hoelmer A. Immunosuppressant therapy in small animal medicine: what, when, and why. *Today's Veterinary Practice*. 2023. V. 13 (4). P. 82–93.
16. Mercer S. W., Gunn J., Wyke S. Improving the health of people with multimorbidity: the need for prospective cohort studies. *Journal of Comorbidity*. 2011. V. 1 (1). P. 4–7. https://doi.org/10.15256/joc.2011.1.10.
17. Food and Drug Administration USA. Initial safety trial results find increased risk of serious heart-related problems and cancer with arthritis and ulcerative colitis medicine Xeljanz, Xeljanz XR (tofacitinib), 2021. URL: https://www fda gov/drugs/drug-safety-and-availability/initial-safety-trial-results-find-increased-risk-serious-heart-related-problems-and-cancer-arthritis.
18. ORAL surveillance investigators. Cardiovascular and cancer risk with Tofacitinib in rheumatoid arthritis. S. R. Ytterberg, D. L. Bhatt, T. R. Mikuls et al. *The New England journal of medicine*. 2022. V. 386 (4). P. 316–326. https://doi.org/10.1056/NEJMoa2109927.
19. Cardiotropic influence of synthetic and genetically-engineered suppressors in rats with experimental rheumatoid arthritis combined with arterial hypertension. N. M. Seredynska, V. I. Korniyenko, K. S. Marchenko-Tolsta et al. *World of Medicine and Biology*. 2020. V. 73 (3). P. 205–210. https://doi.org/10.26724/2079-8334-2020-3-73-205-210.
20. The efficacy and safety of leflunomide for the treatment of lupus nephritis in chinese patients: systematic review and meta-analysis. H. Cao, Y. Rao, L. Liu et al. *PLoS One*. 2015. V. 10 (12). P. e0144548. https://doi.org/10.1371/journal.pone.0144548.
21. Diamantopoulos A. P., Hetland H., Myklebust G. Leflunomide as a corticosteroid-sparing agent in giant cell arteritis and polymyalgia rheumatica: a case series. *BioMed research international*. 2013. V. 2013. P. 120638. https://doi.org/10.1155/2013/120638.
22. Can Leflunomide play a role in cytomegalovirus disease prophylaxis besides its antirheumatic effects? C.-H. Lu, J.-H. Tsai, M.-Z. Wu et al. *Antiviral Therapy*. 2015. V. 20 (1). P. 93–96. https://doi.org/10.3851/IMP2796.
23. Cantarero-Prieto D., Moreno-Mencia P. The effects of gastrointestinal disturbances on the onset of depression and anxiety. *PLoS One*. 2022. V. 17 (1). P. e0262712. https://doi.org/10.1371/journal.pone.0262712.
24. Systematic review: exercise-induced gastrointestinal syndrome – mplications for health and intestinal disease. R. J. S. Costa, R. M. J. Snipe, C. M. Kitic, P. R. Gibson. *Alimentary Pharmacology and Therapeutics*. 2017. V. 46 (3). P. 246–265. https://doi.org/10.1111/apt.14157.
25. Wallace J. L. NSAID gastropathy and enteropathy: distinct pathogenesis likely necessitates distinct prevention strategies. *British Journal of Pharmacology*. 2012. V. 165 (1). P. 67–74. https://doi.org/10.1111/j.1476-5381.2011.01509.x.
26. Effects of medicines used to treat gastrointestinal diseases on the pharmacokinetics of coadministered drugs: a PEARRL Review. C. Litou, A. Effinger, E. S. Kostewicz et al. *Journal of Pharmacy and Pharmacology*. 2019. V. 71 (4). P. 643–673. https://doi.org/10.1111/jphp.12983.
27. Europen convention for the protection of vertebrate animals used for experimental and other scientific purpose: Council of Europe. Strasbourg. 1986. P. 52.
28. Animal models of rheumatoid arthritis. D. L. Asquith, A. M. Miller, I. B. McInnes, F. Y. Liew. *European journal of immunology*. 2009. V. 39 (8). P. 2040–2044. https://doi.org/10.1002/eji.200939578.

29. Моделювання артеріальної гіпертензії шляхом тривалого сольового навантаження. Моніторинг функціонування серцево-судинної системи та динаміки інтегральних показників життєдіяльності у щурів (частина II). Н. М. Серединська, М. А. Мохорт, В. С. Хоменко, К. С. Марченко-Толста та ін. *Фармакологія та лікарська токсикологія*. 2019. Т. 13 (3). С. 203–212. https://doi.org/10.33250/13.03.203ю
30. Antiinflammatory activity of leflunomide for combined application with celecoxib and amlodipine in adjuvant arthritis against the background of arterial hypertension. N. M. Seredynska, V. I. Korniyenko, M. A. Mokhort et al. *World of Medicine and Biology*. 2020. V. 71 (1). P. 218–223. https://doi.org/10.26724/2079-8334-2020-1-71-218-223.
31. Спосіб поглибленої оцінки гастро- та ентеротоксичного впливу як побічної дії ліків різних фармакологічних груп. Н. М. Серединська, К. С. Марченко-Толста, О. С. Суворова, Т. А. Бершова. *Здобутки клінічної і експериментальної медицини*. 2022. № 3. С. 89–101. https://doi.org/10.11603/1811-2471.2022.v.i3.13296.

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## Gastroduodenal effects of leflunomide under experimental adjuvant-induced rheumatoid arthritis and comorbid arterial hypertension

Use of leflunomide (LEF), a synthetic immunosuppressor, for the treatment of rheumatoid arthritis (RA), has become an innovation in the management of the disease. Despite the widely and successfully use of the LEF for RA treatment, its pharmacological properties and side effects are not well understood.

*The aim of the study* was to examine the gastroduodenal effects of prolonged enteral use of the LEF in adjuvant-induced RA and comorbid arterial hypertension (AH).

The experiments were carried out on male and female mature nonlinear rats, which were divided into five groups. The animals of control group (n = 10) were treated with starch suspension, the animals of the second group (n = 15) were injected with complete Freund's adjuvant – adjuvant-induced arthritis (AA), the third group (n = 15) AA and comorbid AH (salt-loading model), the fourth group (n = 15) consisted of animals with AA treated with LEF, the fifth group (n = 15) – animals with comorbid condition (AA + AH), which were treated by LEF. Administering of starch-LEF suspension into the stomach was carried out through a special metal probe to rats with adjuvant-induced arthritis and comorbid pathology once daily for the first 3 days at a dose of 15 mg/kg (shock dose) and then at a dose of 1.5 mg/kg (therapeutic dose) for the next 53 days. After finishing the experiments, gastroduodenal toxic effects of the drug were determined according to the frequency of rats with pathological lesions (hyperemia, petechiae, edema, ulcers) and intensity of the damages using a point scale.

It has been established that prolonged use of the LEF leads to high levels of gastroduodenal toxicity in rats with adjuvant-induced arthritis and combined pathological condition: an increase in the frequency of rats with gastroduodenal mucosal pathology and intensity of various types of damages (petechiae, edema, ulcers). LEF induced higher prevalence of duodenal than gastric toxicity in rats with both adjuvant-induced arthritis and arterial hypertension comorbidity.

Thus, gastroduodenal mucosa pathology after prolonged use of LEF in adjuvant-induced arthritis and comorbid state increases a need for adjuvant therapy to prevent such adverse effects. Moreover, further pharmacological research in order to introduce appropriate drugs is recommended. Furthermore, conducting preclinical and clinical studies to understand the pharmacokinetics, mechanisms of action, and interaction of LEF, in particular, with antihypertensive and gastroprotective agents seem necessary.

Implementation of the results of the study in healthcare practice will help to optimize the treatment regimen for rheumatoid arthritis and comorbidities.

*Key words: leflunomide, gastroduodenal toxicity, rheumatoid arthritis, arterial hypertension, comorbid pathology*

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## Гастродуоденальні ефекти лефлуноміду за експериментального ревматоїдного артриту, коморбідного з артеріальною гіпертензією

Застосування лефлуноміду (ЛЕФ), синтетичного імуносупресора, для лікування ревматоїдного артриту (РА) є інновацією в лікуванні цього захворювання. Незважаючи на широке та успішне застосування ЛЕФ для лікування РА, його фармакологічні властивості та побічні ефекти недостатньо вивчені.

*Мета дослідження* – вивчення гастродуоденальних ефектів тривалого ентерального застосування ЛЕФ у щурів за моделювання ад'ювантного РА та коморбідної артеріальної гіпертензії (АГ).

Експеримент проведено на 70 статевозрілих нелінійних щурах-самцях і самках, розподілених на 5 груп: контрольну (10 щурів) та чотири дослідні по 15 щурів у кожній (модель РА, РА + АГ, РА + ЛЕФ, РА + АГ + ЛЕФ).

Модель РА відтворювали ін'єкцією повного ад'юванта Фрейнда, АГ моделювали в тварин шляхом сольового навантаження.

Після завершення експерименту досліджували слизову оболонку гастродуоденальної зони на наявність пошкоджень (гіперемія, петехії, набряк, виразки), реєстрували частоту їхнього виникнення та оцінювали їх інтенсивність у балах.

1 % крохмально-ЛЕФ суспензію вводили щурам у шлунок через спеціальний металевий зонд один раз на день протягом 3 днів в ударній дозі (15 мг/кг маси тіла) та наступних 53 днів у терапевтичній дозі (1,5 мг/кг).

Встановлено, що тривале застосування ЛЕФ на тлі ад'ювантного артриту, а також коморбідного з АГ призводило до збільшення частоти та інтенсивності різних типів пошкоджень слизової оболонки гастродуоденальної зони. Як у разі ад'ювантного артриту, так і коморбідної патології ЛЕФ виявляв більшу токсичну дію щодо слизової оболонки кишечника, ніж шлунка.

Таким чином, отримані результати свідчать про необхідність ад'ювантної терапії в разі тривалого застосування ЛЕФ для запобігання гастродуоденальним побічним ефектам препарату.

Рекомендовано проведення фармакологічних досліджень з метою впровадження відповідних препаратів. Крім того, необхідні подальші доклінічні та клінічні дослідження для розуміння фармакокінетики, механізмів дії та взаємодії ЛЕФ, зокрема з антигіпертензивними та гастропротекторними засобами. Упровадження результатів дослідження в практику охорони здоров'я допоможе оптимізувати схему лікування ревматоїдного артриту та супутніх захворювань.

*Ключові слова: лефлуномід, гастродуоденальна токсичність, ревматоїдний артрит, артеріальна гіпертензія, коморбідна патологія*

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