ANALYSIS OF THE MAIN DIRECTIONS OF THERAPEUTIC REGIMENS FOR THE TREATMENT OF HELMINTHIASES OF THE DIGESTIVE SYSTEM GIVEN IN THE NEW CLINICAL TREATMENT PROTOCOLS

The treatment of helminthiases of the digestive system is a socially significant problem that is urgent for many countries in the world, including Ukraine. Over the last 5 years, cases of enterobiosis, ascariasis and trichocephalosis have been reported most frequently in Ukraine. Therefore, it is advisable to update and implement the latest treatment protocols for the specified pathology.

Aim. To analyze recommendations for the treatment of helminthiasis of the digestive system, which are given in the new clinical protocols, and identify the promising directions for saturation of the domestic pharmaceutical market with drugs that meet the needs of patients with this pathology.

Materials and methods. The objects of the study were guidelines for the treatment of helminthiases of the digestive system in the open access on the website of the Ministry of Health of Ukraine, scientific publications of domestic and foreign authors and our own research. The methods of generalization, systematization of theoretical and practical material, bibilosemantic and systematic analysis were used in the work.

Results. The study of recommendations for the treatment of enterobiosis, ascariasis, intestinal cestodes, strongyloidosis, nematodosis and trichocephalosis has shown that the drug of choice for the treatment of this group of diseases is albendazole, which is included in each treatment protocol. Mebendazole is recommended for use in all regimens, except for the treatment of strongyloidosis. Drugs of other pharmaceutical ingredients are recommended for administration in rare cases. The main types of the pharmacological activity and side effects of albendazole are given.

Conclusions. The treatment regimens recommended for helminthiasis of the digestive system have been analyzed, and the substances, based on which the development of domestic anthelmintic drugs is rational, have been determined.

Key words: analysis; treatment regimen; clinical protocol; helminthiasis
регистрируются случаи энтеробиоза, аскаридоза и трихоцефалеза. Поэтому целесообразным является обновление и внедрение в использование новейших протоколов лечения указанной патологии.

**Цель работы.** Целью данной работы является анализ рекомендаций по лечению гельминтозов пищеварительной системы, приведенных в новых клинических протоколах, и определение перспективных направлений по насыщению отечественного фармацевтического рынка лекарственными средствами, отвечающими потребностям пациентов с данной патологией.

**Материалы и методы.** Объектами исследования были рекомендации по лечению гельминтозов пищеварительной системы, находящиеся в открытом доступе на сайте Министерства здравоохранения Украины, научные публикации отечественных и зарубежных авторов, собственные исследования. В работе использовались методы обобщения, систематизации теоретического и практического материала, библиосемантического и системного анализа.

**Результаты и их обсуждение.** Изучение рекомендаций по лечению энтеробиоза, аскаридоза, кишечных цепостодов, стронгилоэдоза, нематодоза и трихоцефалеза показало, что лекарственным препаратом выбора для лечения данной группы заболеваний является альбендазол, который указан в каждом протоколе лечения. Мебендазол рекомендован к применению во всех схемах, кроме терапии стронгилоэдоза. Лекарственные препараты других фармацевтических ингредиентов рекомендованы к применению в редких случаях. Для альбендазола приведены основные виды фармакологической активности и побочных эффектов.

**Выводы.** Проанализированы лечебные схемы, рекомендованные для лечения гельминтозов пищеварительной системы, установлены субстанции, на основе которых разработка отечественных противогельминтных лекарственных препаратов является рациональной.

**Ключевые слова:** анализ; схема лечения; клинический протокол; гельминтозы

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**On April 28, 2017, the Order of the Ministry of Health of Ukraine No. 1422 of December 29, 2016, allowing the application of international treatment protocols in the territory of Ukraine came into force. In particular, the Ministry of Health of Ukraine has signed an agreement with the Finnish medical-scientific society Duodecim Medical Publications Ltd, which specializes in comprehensive solutions in the field of evidence-based medicine.**

**Guidelines for the treatment of gastrointestinal helminthiasis are among many clinical protocols proposed for the use and discussion [1-7].**

**The aim of this work is to analyze recommendations for the treatment of helminthiasis of the digestive system and identify the promising directions for saturation of the domestic pharmaceutical market with drugs that meet the needs of patients with this pathology.**

**Materials and methods**

The objects of the study were guidelines for the treatment of enterobiosis, ascariasis, intestinal cestodes, strongyloidosis, nematodiasis, trichocephalosis in the open access on the website of the Ministry of Health of Ukraine, scientific publications of domestic and foreign authors and our own research. The methods of generalization, systematization of theoretical and practical material, bibliosemantic and systematic analysis were used in the work.

**Results and discussion**

The guidelines studied include the description of the infectious agent, the clinical picture of the disease, diagnostic tools, treatment recommendations and references. Thus, the treatment regimens are mostly based on the use of mebendazole, albendazole and ivermectin (Tab. 1).

As can be seen from the results (Tab. 1), each treatment regimen contains recommendations for the use of albendazole. Mebendazole is recommended for use in all regimens, except for the treatment of strongyloidosis. Drugs of the other active pharmaceutical ingredients are recommended for use less often (Fig.).

Thus, albendazole is the drug of choice in the treatment of helminthiasis of the digestive system; it indicates the feasibility of developing domestic anthelmintic agents on its basis. According to the data of the PASS analysis the probability of the anthelmintic and antiparasitic activity of albendazole is greater than 0.8 (Tab. 2).

The mechanism of action of albendazole is in the disorder of the metabolism of helminths. Drugs of benzimidazole group provoke metabolic disorders by selectively binding to β-tubulin and inhibiting polymerization that causes cytoplasmic formation of microtubules.

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Fig. The frequency of recommendations for active pharmaceutical ingredients with the anthelmintic activity in new evidence-based guidelines
However, the mechanism of helminth resistance to benzimidazoles in general and albendazole in particular should be considered: specific changes in amino acids of the β-tubulin protein lead to a decrease in affinity for it, which significantly reduces the pharmacological effect [8].

When developing a new drug the likely side effects of using albendazole should be also taken into account, making every effort to minimize them. In particular, the side effects of albendazole are given in Tab. 3 [9, 10].

In view of the results obtained, it is advisable to focus on the development of domestic medicines.

### Table 1

| Pathology            | Active Pharmaceutical Ingredient | The treatment regimen                                                                 |
|----------------------|----------------------------------|--------------------------------------------------------------------------------------|
| Ascaridosis          | Mebendazole (drug of choice)     | 100 mg twice daily for 3 days (or 500 mg once) for adults and children > 2 years       |
|                      | Albendazole                      | 400 mg once or for 3 days (200 mg once for children < 2 years)                        |
|                      | Ivermectin                       | 0.15–0.2 mg/kg once (Ivermectin as of May 22, 2019, is registered in Ukraine only in the form of ointment with indications for the treatment of inflammatory lesions caused by Rosacea) |
|                      | Piperazine                        | 75 mg/kg (maximum – 4 g) for two consecutive days (used for the purpose of causing flaccid paralysis of worms in intestinal obstruction or obstruction of the bile ducts) |
|                      |                                   | To pregnant women: Piperazine – 75 mg/kg (maximum – 4 g) for two consecutive days     |
|                      |                                   | Pyrantel – 10 mg/kg once                                                                |
| Ostritsa (enterobiosis) | Pirvine                        | 7.5-10 mg/kg once (Pirvine (trade name) with the international non-proprietary name pyrvinium as of 22.05.2019 is not registered in Ukraine) |
|                      | Mebendazole                      | 100 mg once                                                                             |
|                      | Albendazole                      | 400 mg once                                                                             |
| Intestinal cestodes  | Niclosamide                      | 2 g for adults, 1.5 g for children weighing more than 35 kg, and 1.0 g for children weighing 11–34 kg |
|                      | Praziquantel                     | 5-20 mg/kg (As of 05/02/2020, the drugs niclosamide and praziquantel are not registered in Ukraine) |
| Nematodosis          | Mebendazole                      | the dose for adults and children over 2 years old is 100 mg twice daily for 3 days      |
|                      | Albendazole                      | 400 mg once in adults and children over 2 years old                                     |
|                      |                                   | 200 mg once in children under 2 years old                                              |
| Strongyloidosis      | Ivermectin                       | 200 mg kg once a day for 2 days (Ivermectin as of May 22, 2019, is registered in Ukraine only in the form of ointment with indications for the treatment of inflammatory lesions caused by Rosacea) |
|                      | Albendazole                      | 400 mg twice daily for 7 days                                                           |
| Trichocephalosis     | Mebendazole                      | dosage for adults and children over 2 years old is 100 mg 2 times a day for 3 days     |
|                      | Albendazole                      | 400 mg once a day for 3 days (for children under 2 years the dose is 200 mg)            |

### Table 2

The pharmacological activity of albendazole according to the PASS analysis

| Probability of the activity | Type of the pharmacological activity |
|-----------------------------|---------------------------------------|
| 0.847                       | Anthelmintic (nematodes)              |
| 0.834                       | Anthelmintic (general)                |
| 0.826                       | Antiparasitic                         |
Side effects of albendazole

| Common                          | Rare                                          | Isolated cases                       |
|---------------------------------|------------------------------------------------|--------------------------------------|
| Stomach pain, fever, nausea     | Black tarry stool, bleeding gums, blood in urine or feces, chest pain, chills, cough, painful or difficult urination, red spots on the skin, sore throat, ulcers or white spots on lips or mouth, swollen glands unusual bleeding or bruising, unusual fatigue or weakness, dizziness, hair loss | Peeling or weakening of the skin, blurred vision, dark urine, diarrhea, general feeling of fatigue or weakness, headache, joint or muscle pain, light stool, red, irritated eyes, seizures, persistent stomach pain, vomiting, yellow eyes or skin |

for the treatment of helminths of the digestive system on the basis of the above active pharmaceutical ingredients since the effectiveness of their administration is evidence-based. The most promising substance in this case is albendazole as it is present in each of the guidelines studied. Particular attention should be paid to the absence of pirvime, ivermectin and praziquantel-based drugs at the Ukrainian pharmaceutical market. It is also advisable to study the prospects of combining multiple substances in a single dosage form to potentiate the effect.

CONCLUSIONS

1. The regimens proposed for the treatment of helminthiasis of the digestive system in the relevant Guidelines on evidence-based medicine (DUODECIM Medical Publications, Ltd.) presented on the website of the Ministry of Health of Ukraine, have been analyzed.

2. It has been found that albendazole and mebendazole are the drugs of choice for the treatment of parasitic diseases of the digestive system. Medicines of other pharmaceutical ingredients are recommended for use in isolated cases.

3. The mechanism of action and probable side effects of albendazole have been described; they should be taken into account when developing drugs on its basis.

Conflict of interests: authors have no conflict of interests to declare.

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