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STUDY OF THE SAFETY OF ANTIANEMIC PREPARATIONS BY METHOD OF THE SYSTEM OF PROBLEMS RELATED TO MEDICINAL PREPARATIONS

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Iron deficiency is the most common micronutrient deficiency worldwide. Prevention and treatment of iron deficiency conditions are some of the most important health problems in many countries of the world. At the same time, the main problems for it remain the timely diagnosis, elimination of the cause, as well as the choice of replacement therapy with iron-containing drugs and correction of adverse reactions (ADR) that occur during their use.

The aim. This research aims to study the peculiarities of the development of antianaemic drugs ADRs in patients living in the territory of the Republic of Crimea.

Materials and methods. The objects of research were cases of ADR occurrence associated with the use of a group of antianaemic drugs and revealed during the 2009-2018 period in the territory of the Republic of Crimea. The main tasks in the analysis of notification forms were the study of the ADR severity, the causality assessment for suspected drugs and ADRs, as well as analysis of particular problems associated with the use of antianaemic drugs (Drug-related problems, DRP).

Results. Iron supplements in combination with other drugs became the leaders in the incidence of ADR among antianaemic drugs (28 cases, 42.4% of all cases of ADR). The largest number of cases was registered in patients aged from 18 to 30 years, with female patients prevailing. Among the clinical manifestations of ADR, the most cases were drug hypersensitivity reactions of varying severity (40 cases) and disorders of the gastrointestinal tract (18 cases). The study of the problems associated with the use of antianaemic drugs made it possible to determine that the highest rates of DRP values were observed with the use of iron preparations for parenteral use and cyanocobalamine. The minimal DRP values were observed when prescribing iron protein succinylate preparations.

Conclusion. The basis of pharmacotherapy for various types of anemias is the replenishment of iron and vitamin B_{12} (cyanocobalamin) depots. The effectiveness of the treatment in these cases largely depends on the patient's adherence to treatment, which is, in turn, depends on the frequency and severity of ADRs that occur during the use of antianaemic drugs.

Keywords: antianaemic drugs; iron supplements; adverse reactions; drug problems; DRP; dyspepsia

Abbreviations: DRP – Drug-related problems; WHO – World Health Organization; CI – confidence interval; MP – medicinal products; INN – international non-proprietary name; ADR – adverse drug reactions; MSS – musculoskeletal system; CR – causal relationship; DHR – drug hypersensitivity reactions, CNS – central nervous system

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RESEARCH ARTICLE

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ИЗУЧЕНИЕ БЕЗОПАСНОСТИ ПРИМЕНЕНИЯ АНТИАНЕМИЧЕСКИХ ПРЕПАРАТОВ С ИСПОЛЬЗОВАНИЕМ МЕТОДА СИСТЕМЫ ПРОБЛЕМ, СВЯЗАННЫХ С ЛЕКАРСТВЕННЫМИ ПРЕПАРАТАМИ

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Недостаток железа является наиболее распространенным дефицитом питательных микроэлементов во всем мире. Профилактика и лечение железодефицитных состояний является одной из важнейших проблем здравоохранения многих стран мира. Основными проблемами при этом остается своевременная постановка диагноза, устранение первопричины заболевания, а также выбор заместительной терапии препаратами железа и коррекции нежелательных реакций, возникающих при их применении.

Цель. Изучение особенностей развития нежелательных реакций антианемических препаратов у пациентов, проживающих на территории Республики Крым.

Материалы и методы. Объектами исследования являлись зарегистрированные за период 2009–2018 гг. на территории Республики Крым случаи возникновения нежелательных реакций при применении группы антианемических препаратов. Основными направлениями анализа карт-извещений стало изучение серьезности нежелательных реакций, достоверности причинно-следственной связи между подозреваемыми лекарственными препаратами и возникающими нежелательных реакций, а также проблем, связанных с применением антианемических лекарственных средств (Drug related problems, DRP).

Результаты. Лидерами по частоте развития нежелательных реакций среди антианемических препаратов стали препараты железа в комбинации с другими препаратами (28 случаев, 42,4% от всех случаев развития НР). Наибольшее количество случаев было зарегистрировано у пациентов в возрасте от 18 до 30 лет, при этом преобладали пациенты женского пола. Среди клинических проявлений нежелательных реакций преобладали случаи развития реакций лекарственной гиперчувствительности различной степени тяжести (40 случаев) и нарушения со стороны желудочно-кишечного тракта (18 случаев). Изучение проблем, связанных с применением антианемических препаратов, позволили определить, что наиболее высокие показатели значений DRP (DRP=10) наблюдались при применении препаратов железа для парентерального применения и цианокобаламина. Минимальные показатели значений DRP (DRP=6) наблюдались при назначении препаратов железа протеина сукцинилата.

Заключение. Основой фармакотерапии различных видов анемий является восполнение запасов железа и витамина B_{12} (цианокобаламина). Эффективность лечения пациентов при этом во многом зависит от их приверженности к лечению, которая обусловлена частотой и тяжестью нежелательных реакций, возникающих на фоне применения антианемических препаратов.

Ключевые слова: антианемические препараты; препараты железа; нежелательные реакции; проблемы, связанные с лекарственными препаратами; DRP; диспепсия

Список сокращений: DRP – проблемы, связанные с лекарственными препаратами; ВОЗ – Всемирная организация здравоохранения; ДИ – доверительный интервал; ЛС – лекарственные средства; МНН – международное непатентованное название; НР – нежелательные реакции; ОДА – опорно-двигательный аппарат; ПСС – причинно-следственная связь; РЛГ – реакции лекарственной гиперчувствительности; ЦНС – центральная нервная система.

INTRODUCTION

According to the World Health Organization (WHO) data, about 25% of the population worldwide is affected by anemia [1]. Therefore, iron deficiency is one of the most common health problems in the majority of the countries all over the world [2]. The main categories of patients with anemia are preschool children (47.4%; 95% confidence interval (CI) 45.7–49.1), pregnant women (41.8%; 95% CI 39.9–43,8), as well as non-pregnant women of childbearing age (30.2%; CI 28.7–31.6) [2]. Premenopausal women and patients with inflammatory bowel diseases are also high-risk iron loss and anemia groups [3].

The basis of pharmacotherapy for the conditions caused by iron deficiency, is oral and parenteral preparations of ferrous and ferric iron [4]. A high efficiency of these drugs, unfortunately, does not exclude the risk of developing adverse reactions (ADRs) during their use [5]. The oral administration of iron preparations is associated

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with the development of gastrointestinal disorders in patients [6]. This is confirmed by a meta-analysis conducted by Tolkien Z. et al. [3]. In the study, the incidence of constipation in the patients taking oral iron preparations, was 12%; diarrhea was observed in 8%, and nausea – in 11% of patients. This study also revealed that the frequency of gastrointestinal ADRs after peroral use of iron products was twice higher than in the patients of the control group, and 3 times higher than in the patients receiving iron preparations in the parenteral forms [3].

The administration of parenteral forms of iron preparations is much less frequently associated with gastrointestinal tract disorders. However, the risks of severe pseudoallergic reactions (the incidence of 1/200000 cases), manifested by severe hypotension, loss of consciousness, urticaria, and bronchospasm, are not excluded [7].

THE AIM is to study the development peculiarities of the adverse reactions (ARs) of antianemic drugs in the patients living in the territory of the Republic of Crimea.

MATERIALS AND METHODS

The objects of the study were ADRs cases registered for the period 2009–2018 in the territory of the Republic of Crimea, associated with the use of antianemia drugs. The information about ADRs for the chosen group of medicinal preparations (MPs) was extracted from the Autonomic Database of Adverse Reactions in Crimea (ARCADe – Adverse Reactions in Crimea, Autonomic Database). These were spontaneous reports. Database has a limited access.

The identification of adverse reactions to antianemia drugs was carried out using the codes of the Anatomical Therapeutic Chemical (ATC) classification of WHO[1] (ATC/DDD, Index 2019 (available at: https://www.whocc.no/atc_ddd_index/), Summary of Product Characteristics (SmPC) data from the State Registers of Medicines of the Russian Federation and Ukraine (for the cases registered before the accession of the Republic of Crimea to the Russian Federation). In accordance with the ATC classification, antianemia drugs have been assigned the B03 code. The studied pharmacological group includes the groups of iron preparations (B03A), vitamins B12 and folic acid (B03B), and other antianemia drugs (B03X).

The analysis of the ADRs severity was carried out in accordance with Article 4 of Federal Law No. 61-FZ dated April 12, 2010 «On the Circulation of Medicines»[2].

The study of the causal relationship (CR) reliability was carried out in accordance with the algorithms of Naranjo and Karch F.E., Lasagna L.[3] [8]. In accordance with the Naranjo algorithm, a degree of CR is assessed by a certain number of points received when answering a questionnaire. The degree of reliability, expressed in points, is classified as follows: certain (9 or more points), probable (5–8 points), possible (1–4 points), doubtful (0 or fewer points). Evaluation of CR using the Karch-Lasagna algorithm assumes an answer to 5 questions with their scoring and the selection of 5 main CR categories: certain (8 or more points), probable (6–7 points), possible (4–5 points), conditional (1–3 points), unlikely (0 or fewer points).

The type of adverse reactions was determined using two main classifications: the WHO (Rawlins-Thomson) classification and the Will-Brown one [9]. In accordance with the WHO classification, 6 main types of ADRs are distinguished (type A – dose-dependent ADRs, type B – dose-independent ADRs, type C – ADRs associated with a prolonged use of drugs, type D – delayed reactions, type E – withdrawal reactions, type F – 'no effect' reactions). The Williams and Brown classification includes 9 types of ADRs: type A – augmented dose-dependent, passing when the drug is withdrawn or its dose is reduced; type B – the action on microorganisms (for example, antibiotics administration causes candidiasis); type C – chemical/chronic ones, concentration-dependent; type D – ADRs associated with the delivery method or a drug form (for example, the occlusion of blood vessels by drug particles), type E – withdrawal reactions, physical dependence; type F – familial, reactions caused by a congenital metabolic defect; type G – a genetic damage; type H – hypersensitivity reactions; and type U – unclassified. The classification of ADRs proposed by the WHO is based on the predictability of ADRs and dose-dependence. The use of the Williams and Brown classification allows to more fully characterize ADRs, including the identification of the ones caused by a genetic damage, congenital metabolic defects, and the effect of a drug on microorganisms.

The second stage of the analysis of ADRs notification cards for antianemia drugs, was the study of problems associated with the use of drugs (Drug-related problems, DRPs). According to the Pharmaceutical Care Network of Europe (PCNE), a DRP is defined as "an event or circumstance associated with drug therapy that actually or potentially prevents the patient from achieving the desired results of pharmacotherapy"[4] [10–14]. The DRPs analysis was carried out using the updated version of the DRPs qualification system PCNE V9.0 [13], which allows assessing the problems, causes and interventions associated with DRPs [19]. The benefit of the ninth version of the PCNE V 9.0 system is the inclusion of category A (Acceptance) – "Interventions acceptance", in the analysis. The options for accepting interventions (code «A») are as follows: the intervention is acceptable, the intervention is not acceptable, or there is no information about the adoption of certain interventions.

[1] ATC/DDD Index 2019. Available at: https://www.whocc.no/atc_ddd_index/

[2] Federal Law of the Russian Federation No.61-FZ dated April 12 for 2010 "On the Circulation of Medicines". Electronic resource: http://www.consultant.ru/document/cons_doc_LAW_99350/ (link active on 10.12.2019).

[3] Standard operating procedure for monitoring the effectiveness and safety of drugs in medical organizations of the state healthcare system of the Moscow for general practitioners and nurses. Guidelines. – Edited by M.V. Zhuravleva. – Moscow. – 2019. 42 p.

[4] PCNE Classification for Drug-Related Problems V9. Available from: https://www.pcne.org/upload/files/417_PCNE_classification_V9-1_final.pdf)

The evaluation of the obtained DRPs results makes it possible to identify the main factors contributing to the development of complications after the use of drugs. Among such factors, an irrational choice of drugs, a violation of the dosage regimen, and the lack of taking into account the possible drug-drug interaction, can be singled out. The ADRs cases characterized by low DRPs indices, indicate a relative safety of pharmacotherapy for the patient. To determine the boundaries of the confidence intervals, the Clopper-Pearson method was used [15].

Each case of ADRs associated with the use of antianemia drugs was assessed by three researchers (Matveev A.V., Egorova E.A., Bekirova E.Yu.), in case of disagreement between them, the opinion of the fourth expert (Koniaeva E.I.) was taken into account.

RESULTS

To analyze the adverse reactions associated with the use of antianemia drugs (ATC code B03), 66 reports (2009–2018) were selected from the ARCADe regional database, which amounted to 0.96% of the total number of ADR cases registered for the corresponding period in the Republic of Crimea (6843 notification cards). The distribution of antianemia drugs by pharmacological groups was as follows: 53 cases (80.3%) of ADRs to iron preparations and 13 cases (19.7%) to vitamin B12 and folic acid preparations (Table 1).

It is important to note a high incidence of ADRs to iron supplements in combination with other drugs (28 cases, 42.4% of all cases of ADRs to antianemia drugs). Among sporadic representatives of combined drugs, the leader in the incidence of ADRs was a combination of iron sulfate (II) and ascorbic acid – 20 cases, less often ADRs were caused by the use of a combination of iron gluconate dihydrate and manganese and copper gluconate – 5 cases. Two cases were associated with the use of a combination of iron fumarate, cyanocobalamin, folic acid, pyridoxine hydrochloride, and sodium docusate; and 1 case was associated with the use of a complex of iron ammonium citrate with folic acid and cyanocobalamin.

The study of the gender characteristics of the ADRs developed after antianemia drugs, made it possible to determine that the majority of ADRs cases were observed in female patients (50 cases, 83.3%), which may be associated with a higher incidence of iron deficiency anemia caused by menstrual blood loss, childbirth, and lactation [16].

The analysis of the age categories of patients with registered antianemia drugs ADRs, was of scientific interest too. In 4 cases (4.5% of the total number of cases), ADRs were observed in pediatric patients (from 0 to 18 years old). In the remaining 62 notification cards, ADRs were observed in patients over 18 years of age. The distribution of the ADRs incidence rate in this age group is shown in Fig. 1.

The analysis of administration ways of antianemia drugs in patients with clinical manifestations of ADRs revealed the prevalence of the oral administration (43 cases, 65.2%). Much less often drugs were administered parenterally (intravenously – 4 cases, 6%; intramuscularly – 15 cases, 22.7%). In 4 cases, there was no information on the administration way of the suspected drugs.

Among the clinical manifestations of ADRs that occur in patients against the background of antianemia drugs, the cases of development of drug hypersensitivity reactions (DHSRs) of varying severity prevailed: urticaria, skin hyperemia – 36 cases (54.5%); angioedema – 2 cases (3.0 %); and anaphylactic shock – 2 cases (3.0%). In 18 cases (27.3%), patients had various clinical gastrointestinal tract symptoms (bloating, diarrhea, nausea, spastic pain). Hemodynamic disorders (weakness, hypotension) and disorders of the central nervous system (headache, dizziness) were observed much less frequently (3 cases of ADRs). The distribution of the remaining cases of ADRs according to their clinical manifestations is shown in Fig. 2.

The obtained data confirm the results of other studies on the possibility of DHSRs after a parenteral use of iron [17–20], which requires careful monitoring of the patient's condition during the infusion, and timely recognition and immediate medical intervention in case of acute hypersensitivity reactions.

A high incidence of DHSRs necessitated an additional analysis of cases based on concomitant allergic anamnesis of patients (household, contact or drug allergies). The number of patients with an allergic anamnesis was 2, in the remaining patients (64 cases) the allergic anamnesis was not complicated.

Another important factor contributing to the development of ADRs, is a simultaneous prescription of 2 or more drugs. According to Thong B. et al., the number of prescribed drugs is one of the most significant risk factors for ADRs development [21]. The results of the analysis of the notification cards made it possible to reveal that in most cases (32 cases, 48.5%) antianemia drugs were used as monotherapy, in 14 cases (21.2%) 1 concomitant drug was included in the patient's therapy list. Less frequently, a simultaneous prescription of 3 or more drugs was observed: 2 concomitant drugs – 5 cases (7.6%), 3 concomitant drugs – 8 cases (12.1%), 4 concomitant drugs – 4 cases (6.1%), 5 concomitant drugs – 2 cases (3%), and 6 concomitant drugs – 1 case (1.5%).

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Table 1 – Distribution of ADR cases by representatives of antianemia drugs

Drug	ATC-code	Amount of records, abs.	Amount of records, % of total antianemia drugs
Iron (II) products for peroral use			
Ferrous fumarate	B03AA02	5	7.6
Ferrous sulfate	B03AA07	2	3.0
Iron (III) products for peroral use			
Iron preparations for oral administration	B03AB	3	4.6
Iron (III) hydroxide polymaltose	B03AB05	2	3.0
Iron protein succinylate	B03AB09	2	3.0
Iron products for parenteral use			
Iron preparations for parenteral use	B03AC	11	16.7
Iron products in combinations with other products			
Iron products in combinations with other products	B03AE10	28	42.4
Cyanocobalamin and Folic acid			
Cyanocobalamin	B03BA01	12	18.2
Folic acid	B03BB01	1	1.5

Table 2 – Median, maximum and minimum DRPs values for antianemia drugs ADRs

Drug	Minimal DRP	Maximal DRP	Median DRP	Range
Iron (II) and iron (III) products for peroral use				
Ferrous fumarate	10	8	9	2
Iron preparations for per-oral use	9	9	9	0
Ferrous sulfate	9	10	9.5	1
Iron (III) hydroxide polymaltose	9	10	9.5	1
Iron protein succinylate	6	6	6	0
Iron products for parenteral use				
Iron products for parenteral use	6	12	10	6
Iron products in combinations with other products				
Iron products in combinations with other products	8	10	9	2
Cyanocobalamin and Folic acid				
Cyanocobalamin	9	14	10	5
Folic acid	10	10	10	0

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Table 3 – Total indices of the median, maximum and minimum values of DRPs for antianemia drugs ADRs in accordance with the standard qualification categories

Drug	Category "P"	Category "C"	Category "I"	Category "A"	Category "O"	Total DRP
Iron (II) and iron (III) products for peroral use						
Ferrous fumarate	1 (1:1)	1 (1:1)	5 (4:6)	1 (1:1)	1 (1:1)	9 (8:10)
Iron preparations for peroral use	1 (1:1)	1 (1:2)	5 (4:5)	1 (1:1)	1 (1:1)	9 (9:9)
Ferrous sulfate	1 (1:1)	1 (1:1)	5.5 (5:6)	1 (1:1)	1 (1:1)	9.5 (9:10)
Iron (III) hydroxide polymaltose	1 (1:1)	1 (1:1)	5.5 (5:6)	1 (1:1)	1 (1:1)	9.5 (9:10)
Iron protein succinylate	1 (1:1)	1 (1:1)	2 (2:2)	1 (1:1)	1(1:1)	6 (6:6)
Iron products for parenteral use						
Iron products for parenteral use	1 (1:1)	1 (0:3)	6 (2:7)	1 (1:1)	1(1:1)	10 (6:12)
Iron products in combinations with other products						
Iron products in combinations with other products	1 (1:1)	1 (1:1)	5 (4:6)	1 (1:1)	1 (1:1)	9 (8:10)
Cyanocobalamin and Folic acid						
Cyanocobalamin	1 (1:2)	1 (1:4)	6 (5:7)	1 (1:1)	1 (1:1)	10 (9:14)
Folic acid	1 (1:1)	1 (1:1)	6 (6:6)	1 (1:1)	1 (1:1)	10 (10:10)

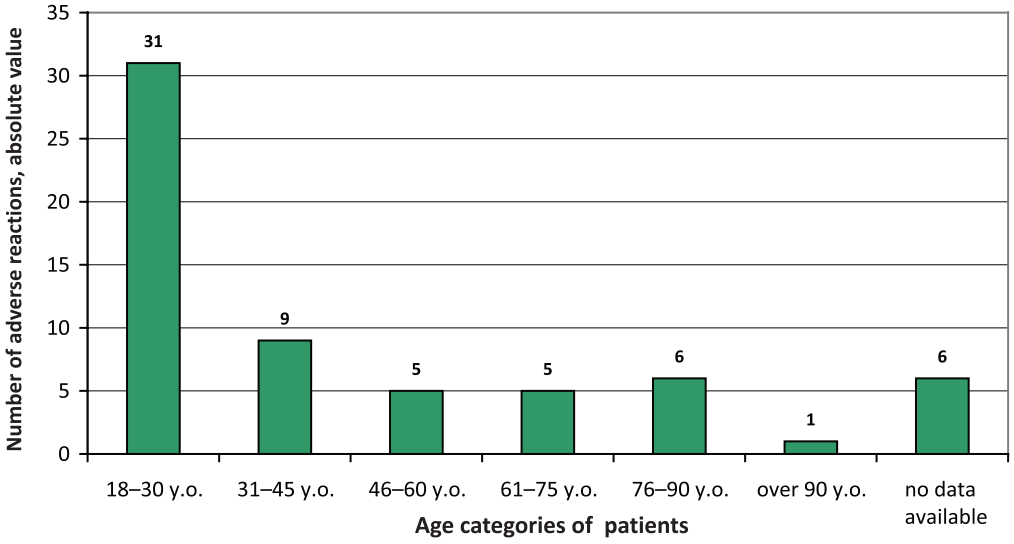

Figure 1 – Distribution of antianemia drugs ADRs in accordance with the age categories of patients

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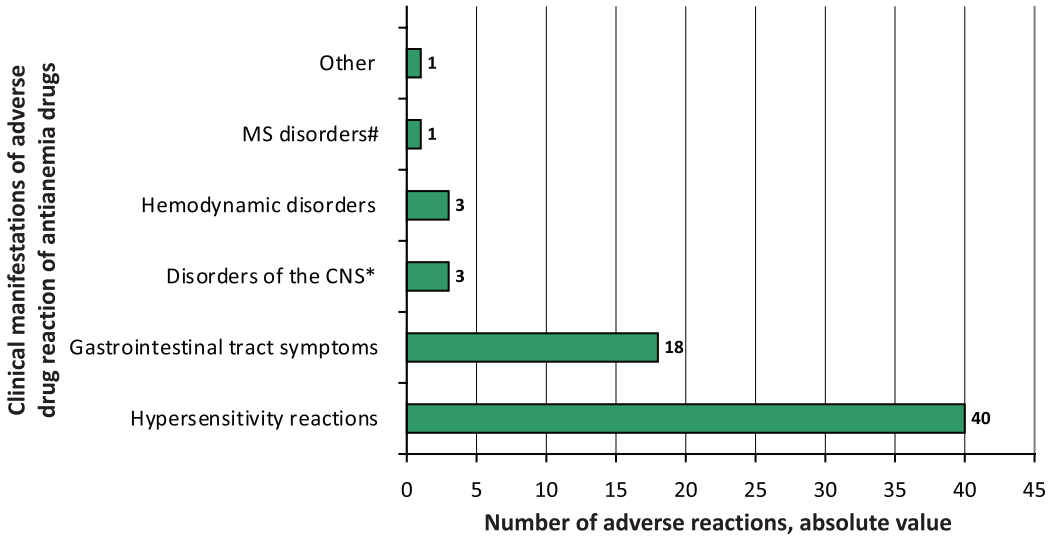

Figure 2 – Distribution of antianemia drugs ADRs in accordance with their clinical manifestations

Note: * – central nervous system, # – musculoskeletal disorders

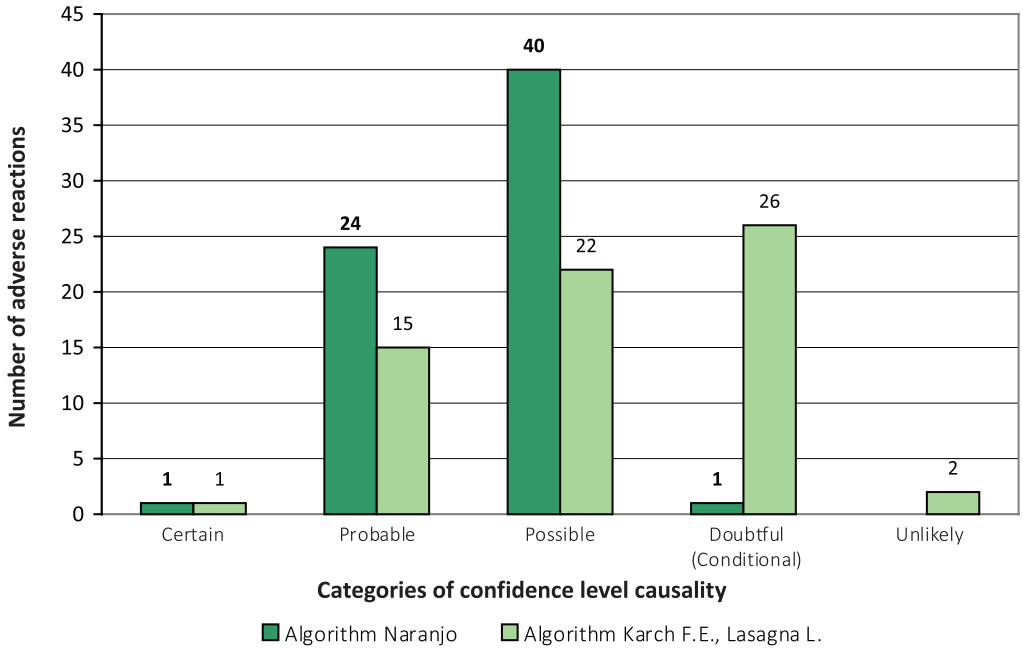

Figure 3 – Distribution of antianemia drugs ADRs in accordance with the degree of reliability of the causal relationship by the Naranjo and Karch F.E.-Lasagna L. algorithms

An important stage in assessing the safety of antianemia drugs is the identification and assessment of serious ADRs, which require a timely discontinuation of the drug therapy, hospitalization of the patient, and/or emergency pharmacotherapy. In accordance with the Federal Law of the Russian Federation No. 61-FZ dated April 12, 2010 «On the Circulation of Medicines», the category of serious adverse reactions includes such ADRs that lead to death, hospitalization, or prolongation of its terms, disability, or congenital anomalies, or a threat to the lives of patients[2].

The distribution of antianemia drugs ADRs in accordance with the criteria of their severity was represented by the following results: a threat to the patient's life – 4 cases (6.1%), temporary disability – 3 cases (4.5%), the need for hospitalization or prolongation of its terms – 4 cases (6.1%). Life-threatening conditions (2 cases of anaphylactic shock and 2 cases of angioedema) were caused by the administration of an iron (III) hydroxide sucrose complex (2 cases), iron (III) hydroxide polymaltose (1 case), and a combined preparation of iron (1 case for iron fumarate + cyanocobalamin + folic acid+ pyridoxine + sodium docusate). The need for hospitalization or its prolongation was due to the development of DHSRs in the form of a confluent rash, as well as severe dyspeptic ADRs (nausea and vomiting).

For the studied group of drugs, the incidence rate of serious ADRs was 8 cases (12.1%), which indicates a high degree of antianemia drugs safety. This is of particular importance in connection with the need for long-term anemia pharmacotherapy. The average duration of an oral iron supplementation course in iron deficiency anemia, ranges from 3 (mild IDA) to 6 months (severe IDA)[5] [22].

The study of the frequency and characteristics of pharmacological correction prescribed by doctors to stop antianemia ADRs made it possible to obtain the following results: the need for medical correction was necessary in 30 cases of ADRs (45.5%), in the remaining 36 cases (54.5%) additional drugs for the relief of ADRs clinical symptoms were not necessary. The main methods of the ADRs correction were antihistamines of the 1st and 2nd generations (Diphenhydramine, Chloropyramine hydrochloride, Loratadine), systemic glucocorticosteroids (Prednisolone, Dexamethasone, Hydrocortisone), and antiemetics.

The assessment of the drug safety also includes determining the degree of CR between the clinical and pharmacological characteristics of the drug and the clinical manifestations of ADRs[3] [8]. It is important to note that at the current moment a CR determination is the most important stage in the assessment of ADRs reports, which is carried out in national and regional pharmacovigilance systems in many countries of the world [23].

In this study, the causality assessment was carried out using the Naranjo and Karch F.E.-Lasagna L algorithms. The results of the CRs assessment of antianemia drugs and the undesirable consequences for patients, are presented in Fig. 3. The most frequent validation categories of CRs, according to the Naranjo algorithm, were probable and possible CRs. This factor indicates the presence of a validation relationship between the use of a drug and an ADR. The analysis of the notifications cards using the Karch F.E. and Lasagna L. algorithm, revealed a high frequency of possible and doubtful CRs, which could be explained by the absence of the time of an ADR occurrence as well as the lack of information on the results of re-challenge of the suspected drug.

The study of ADRs types was carried out using the WHO classification and the Williams and Brown classification. The analysis of ADRs types in accordance with the WHO classification made it possible to determine that in 42 cases (63.3%) there were dose-independent reactions (type B), in the remaining 24 cases there were dose-dependent ADRs (type A). The distribution of ADRs by type in accordance with the Williams and Brown classification made it possible to obtain similar results: hypersensitivity reactions (type H) were observed in 42 cases, and augmented, dose-dependent ones (type A) – in 24 cases.

[5] National standard of the Russian Federation. Patient management protocol. Iron-deficiency anemia. (Electronic resource). Available from: http://docs.cntd.ru/document/1200068753

In the study of the ADRs associated with the use of antianemia drugs, the next stage was the study of drug-related problems (DRPs) [29]. The calculation of the total DRPs values for the ADRs cases made it possible to obtain the following results: DRPs values within 5-8 points were observed in 11 cases (6 DRPs – 6 cases, 7 DRPs – 1 case, and 8 DRPs – 4 cases). In most of the notification cards the number of DRPs was in the range of 9-10 (25 cases, respectively). In 6 cases, the DRPs values were higher than 11 (11 DRPs – 2 cases, 12 DRPs – 2 cases, 13 DRPs – 1 case, and 14 DRPs – 1 case). These factors may indicate the likelihood of incorrect selection of doses when prescribing antianemia drugs or an irrational choice of the drug itself. The total number of DRPs for all cases of ADRs was 623 DRPs; therefore, the average number of DRPs per patient is 9.4 DRPs.

Further on, a quantitative analysis of the problems related to the use of various antianemia drugs was carried out according to the main categories of the ATC classification. For each group of antianemia drugs, the minimum and maximum values, as well as the median DRPs, were calculated (Table 2).

The study of sporadic categories of the DRPs system («P», «C», «I», «A», «O») revealed that for all the studied drugs, the maximum number of problems associated with drugs, was recorded in the section «I» (Interventions). High DRPs values in the presented cases may be due to the interventions on behalf of the doctor in the form of withdrawal or reduction of the dose of the suspected drug and the prescription of additional pharmacotherapy to correct the ADRs.

The analysis of the final DRPs values for each antianemia drug showed that the maximum DRP value was observed for parenteral iron products (10 DRPs), cyanocobalamin (10 DRPs), and folic acid (10 DRPs) (Table 3). The study of these cases confirmed the irrational prescription of cyanocobalamin in chronic pancreatitis (self-treatment) and the irrational prescription of iron for the lumbar dystopia of the right kidney, which caused such high rates. The minimum DRPs values (6 problems) were observed with the use of the same agents. Such ADRs were associated with allergic reactions in case of their rational prescription.

The results of the analysis presented in Table 3 show that the largest range between the minimum and maximum DRPs values was usual for parenteral iron products (max:min – 6:12), and the lowest for iron protein succinylate (max:min – 6:6), peroral iron drugs (9:9) and folic acid (10:10).

DISCUSSION

The study of safety criteria for antianemia drugs, including iron preparations, is an urgent problem all over the world. This is primarily due to the fact that iron deficiency anemia is a clinical symptom of many diseases, such as chronic renal failure, cancer, chronic heart failure, and inflammatory bowel disease [25].

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The research by Goodnough L.T. (2012) confirms the authors' results on a high rate incidence of gastrointestinal ADRs after the use of oral forms of iron products. According to the authors' data, the incidence of such disorders was more than 30% among the treated patients [26]. A parenteral administration of iron drugs, according to data of foreign researchers, is characterized by a less favorable safety profile. First of all, an intravenous administration of iron drugs may be associated with the risk of anaphylactic reactions [27; 28]. According to Szebeni J. et al. (2015), the prevalence of hypersensitivity reactions after a parenteral administration of iron products is about 0.1% [29]. A higher incidence of hypersensitivity reactions (1.4%) associated with the use of iron, was determined in a retrospective study conducted by Australian researchers. They had analyzed the medical records of patients in the municipal healthcare network in the period from January 1, 2010, to December 31, 2019 [30].

The researchers distinguish the following main risk factors for the development of hypersensitivity reactions after the administration of iron preparations: a rapid rate of iron infusion, an allergic anamnesis of the patient, severe atopy, and systemic inflammatory diseases [31]. Numerous studies have also confirmed the authors' data on a more frequent development of serious hypersensitivity reactions in female patients, which is due to the high prevalence of anemia and the need to prescribe iron supplements to this category of patients [32]. In this case, the study by Qassim A. et al. (2018) aimed at studying the efficacy and safety of an intravenous administration of iron polymaltosate preparations in the treatment of iron deficiency during pregnancy, should be mentioned. A retrospective cohort study of 213 pregnant women was conducted from January 2014 to January 2016 at a tertiary clinical hospital. The data on the ADRs development related to iron supplements, were collected from medical papers and electronic records. The results of the study confirmed a rather high rate incidence of ADRs after an intravenous administration of drugs (23.5%), the main of which were local reactions at the administration site (n = 8; 16%), headache (n = 8; 16%), symptomatic hypotension (n = 8; 16%), back pain (n = 7; 14%), and heartburn (n = 6; 12%). In one case, the administration of iron polymaltosate was associated with a severe anaphylactic reaction, manifested by wheezing, chest tightness, and an increased blood pressure. It should be noted that 32 women (15%) experienced side effects requiring discontinuation of treatment and therapy of ADRs symptoms [33].

Another adverse consequence of the use of parenteral iron-containing medicinal products is the ability to reduce chemotaxis as well as the ability of polymorphonuclear cells to the phagocytic activity, which leads to an increase in the risk of infectious processes [32]. The authors' retrospective study of spontaneous messages in the Republic of Crimea did not reveal such ADRs, which may be due to a rather low frequency rate, as well as the severity of their recognition at the post-authorization stage.

The results of the other studies confirm a low incidence rate of ADRs associated with the use of antianemia drugs. However, a parenteral administration of iron preparations can be accompanied by the development of severe anaphylactic reactions that threaten the life of patients, and requires a timely emergency aid to patients with such manifestations of ADRs.

CONCLUSION

The analysis of the ADRs notification cards, recorded in the Republic of Crimea, made it possible to reveal that the most frequent causes of ADRs development in the group of antianemia drugs, are combined iron preparations. The most common clinical manifestations of ADRs were drug hypersensitivity reactions (40 cases) and dyspeptic disorders (18 cases). The frequency rate of serious adverse reactions was 8 cases (12.1% of the total number of ADRs), which indicates a fairly high safety profile of antianemia drugs.

The study of the problems related to the use of antianemia drugs determined that the highest rates of DRPs values were observed during the parenteral use of iron preparations, use and cyanocobalamin. The minimum indicators of DRPs values were observed in the prescription of iron protein succinylate products.

The optimization of pharmacotherapy and prevention of DRPs makes it possible to reduce the incidence rate of ADRs, and significantly increase patient adherence to the treatment, which is essential for long-term maintenance therapy of iron deficiency and megaloblastic anemias.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

A.V. Matveev – work at the concept and design of the study, statistical processing of the results, translation; E.A. Egorova – statistical processing of the results, text writing; E.I. Konyaeva – text writing, editing; E.Yu. Bekirova – text writing, statistical processing of the results; L.A. Adzhimamutova – processing of the research results.

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