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Analysis of side effects of calcium antagonists and determination of ways to minimize them*National University of Pharmacy, Kharkiv*

Key words: cardiovascular diseases, calcium antagonists, side effects, optimization of pharmacotherapy

Cardiovascular diseases are the main cause of death worldwide. Since 2000, the number of deaths from cardiovascular diseases has increased by more than 2 million, and in 2019 it reached almost 9 million. Today, cardiovascular diseases account for 16% of all deaths in the world. Arterial hypertension, ischemic heart disease, tachyarrhythmias, and cerebrovascular disorders are the most common diseases of the cardiovascular system [1].

According to the World Health Organization, the development of side effects (SE) of drugs is one of the serious medical problems. The relevance of this problem is proven by numerous statistical data obtained in different countries of the world. Adverse drug reactions are an integral part of the spectrum of pharmacological action of any, even the most selective drug [2].

Prevention of SE of drugs is one of the most important tasks of practical medicine, which allows improving the quality of medical care for the population. The prevention or minimization of SE is one of the most important tasks of practical medicine, which allows improving the quality of medical care for the population, and the wide application of the analysis of satisfaction with the availability and quality of medical care gives health authorities the most important additional tool necessary for the assessment of health

care technologies in order to make management decisions about priority areas financing [2, 3].

Calcium antagonists (CA) or blockers of slow calcium channels are one of the groups of drugs of first choice for the treatment of arterial hypertension, ischemic heart disease, and tachyarrhythmias. These drugs began to be used in cardiology from the mid-70s, they quickly gained so much popularity that in most developed countries they occupied one of the first places in terms of prescription frequency among drugs used for the treatment of cardiovascular diseases. This is due, on the one hand, to the high clinical effectiveness of calcium antagonists, on the other hand, to the relatively small number of contraindications to their use and the relatively small number of SE caused by them [4–7]

Because of a broad range of pharmacological effects, CA have been used in therapeutic practice for a long time and are well known to practical doctors. The basis for the widespread use of CA was their ability to relax the smooth muscles of the walls of muscular-type arteries and arterioles and thus reduce the overall peripheral resistance [8–12].

The above made it necessary to conduct an analysis of SE of CA, study the assortment of CA on the pharmaceutical market of Ukraine, analyze the evidence base, clinical effectiveness of drugs and determine ways to minimize their SE.

The aim of the study – to analyze the SE of CA in Kharkiv and Kharkiv

region for the period of 2017–2021 and to provide recommendations for their minimizations, to conduct an analysis of the assortment on the Ukrainian pharmaceutical market, an analysis of the evidence base and clinical effectiveness of CA.

Materials and methods. We analyzed the assortment of calcium channel blockers registered in Ukraine, as of March 2023, using the state register of medicinal products of Ukraine [13]. We conducted an analysis of SE of CA with the help of notification cards about adverse reactions in Kharkiv and Kharkiv region for the period of 2017–2021. The study was conducted using passive pharmacovigilance (method of spontaneous reports) from health care facilities of Kharkiv and Kharkiv region. The notification cards were provided by employees of the Kharkiv pharmacovigilance department of the SE «State Expert Center of the Ministry of Health of Ukraine» from the database of the automated information system for pharmacovigilance (AISP). Notification cards about adverse reactions and/or lack of effectiveness of medicinal products during their medical use were filled out in form 137/0, in accordance with the current legislation, orders of the Ministry of Health of Ukraine dated 12.27.2006 No. 898 «On approval of the procedure for conducting pharmacovigilance» (with changes), registered in the Ministry of Justice of Ukraine on 01.29.2007 under No. 73/13340 and dated 04/05/2018 No. 620 «Instruction. Medicines. Proper practices of pharmacovigilance».

Based on the analysis of the evidence base of clinical effectiveness, we determined the conditions of rational use and ways to minimize the SE of CA. To analyze the clinical effectiveness and conditions of rational use of CA, well-known databases were used: Cochrane

Library, Trip Database, and PubMed. These databases contain systematized primary or secondary information on a specific clinical issue: the effectiveness and safety of various medical technologies.

Results and discussion. The first stage of our research was devoted to determining the place of CA among all drugs affecting the cardiovascular system available on the pharmaceutical market of Ukraine during 2022. To conduct the research, we used the state register of medicines of Ukraine.

As of March 20, 2023, 11 522 trade names of drugs were registered in Ukraine. Of them, 3854 are of domestic medicines, 7668 are foreign. 743 trade names of drugs of various groups affecting the cardiovascular system are registered. Of these, 58 names are β -adrenoblockers, 228 monocomponent and combined drugs affecting the renin-angiotensine-aldosterone system (RAAS), 23 antiarrhythmics, 83 – hypolipidemic, 23 names of peripheral vasodilators, 23 – nitrovasodilators, 9 – α 1-adrenoblockers, 93 – diuretics, etc. As of March 20, 2023, 65 trade names of CA were registered in Ukraine [13, 14]. This is 8,7% of all cardiac drugs.

CA are also part of a number of combined antihypertensive drugs. On the pharmaceutical market, there are 23 drugs containing CA + an ACE inhibitor (for example, equator, liram, tarka, etc.), 15 drugs containing CA + an angiotensin II receptor antagonist (for example, combisart, sevikar, teldipine), 1 combination with β -adrenoblocker (alotendin), 1 combination with a diuretic (arifam) [14]. That is, single-component and combined drugs containing CA are up 14% of the assortment of drugs that affect the cardiovascular system.

At the second stage of research, we analyzed the assortment of CA in

Ukraine. As of March 2023, 9 international non-patented names (INNs) of CA were registered on the pharmaceutical market of Ukraine, of which 7 INNs are dihydropyridine derivatives, 1 each is phenylalkylamine and benzothiazepine derivatives. There are 65 trade names of calcium channel blockers on the Ukrainian market, 59 of them are dihydropyridine derivatives. By the number of trade names, amlodipine drugs prevail – 38, nifedipine drugs – 8, lercanidipine – 6, nimodipine – 5, nitrendipine – 1, felodipine – 1 are registered, verapamil – 4, diltiazem – 2 trade names are registered [14]. Among the registered CA, 61.5% are drugs of Ukrainian manufacturers, 38.5% are foreign drugs. The drugs are presented on the market in 4 dosage forms: tablets, capsules, oral drops, solution for injections.

The next stage of our research was devoted to the analysis of 9512 reports of adverse reactions of calcium channel blockers received in 2017–2021 from 145 health care facilities in Kharkiv and Kharkiv region.

The results obtained showed that during 2017–2021, 195 notification cards with cases of adverse reactions to CA were received from health care institutions of Kharkiv region and Kharkiv, of which 59 and 61 notification cards were received in 2017 and 2018, 53 notification cards in 2019, 12 notification cards in 2020, 10 notification cards in 2021 (table 1).

From the analysis of the received cards-notifications, it can be seen that 49 (25,1%) of them were reports about

SE of calcium channel blockers in men, 146 – in women (74,9%). According to the age of the patients, the recorded SE of CA are distributed as follows. 45 cards-notifications regarded to patients under 60 years of age, which is 23% of the total amount of information. 60 cards-notifications were related to patients aged from 61 to 70 years. This is equal to 30.8% of the total number of cards. 68 cards-notifications came from patients aged 71 to 80 years (34.9%), 22 cards-notifications – from patients over 80 years old.

The analysis of cards-notifications revealed that among CA in 2017, the maximum number of adverse reactions was registered for such drugs as Amlodipine-Astrafarm, Amlodipine-KV, Amlodipine-Farmak, Amlodipine-Zdorovya. In 2018, Amlodipine-Astrapharm, Amlodipine-KV, Amlodipine-Farmak were also the leaders in terms of the number of notification cards, in 2019 – Amlodipine-Farmak, Aladin and Amlodipine-KV, in 2020 – Amlodipine, Technolog, in 2021 – Amlodipine-KV and Amlodipine-Zdorovya.

The monitoring of SE to CA for the period 2017–2021 showed that the largest number of reports of adverse reactions was recorded in the form of swelling of the lower extremities in the area of the ankle joints (65.5%). The following side reactions were also recorded: allergic skin reactions (9.5%), tachyarrhythmia (6.4%), nausea (1.8%), headache (3.2%), dry cough (3.2%), redness of the face, feeling of heat (2.3%), hypotension (1.4%) and others (table 2). These adverse reactions did

Table 1

The number of side effects of calcium antagonists during 2017–2021 in health care institutions of Kharkiv and Kharkiv region

Number of cards-notifications				
2017	2018	2019	2020	2021
59	61	53	12	10

Table 2

Monitoring of the frequency of side effects of calcium channel blockers during 2017–2021 in health care institutions of Kharkiv and Kharkiv region

Side effects	The number of registered side effects				
	2017	2018	2019	2020	2021
Edemas of the lower extremities	48	45	37	8	6
Edemas of face	2		1		
Tachyarrhythmia		5	8	1	
Hypotension		3			
Rash on the skin	3	6	4	1	1
Itching of skin	3	1		1	1
Angioedema	1		1		
Headache	3		2	1	1
Dizziness			1	2	
Insomnia		1	1		
Tinnitus			2		
Paresthesias				1	
Dry cough	1		5		1
Nausea	1	3			
Nocturia	1				
Redness of the face, feeling of heat	1	2	1		1
Total number of side effects	64	66	63	15	12

not require additional hospitalization and did not cause disability of the patients.

Analysis of cards-notifications with cases for 5 years showed that the majority of SE in the form of edemas of the legs, redness and rash on the skin, itching, tachyarrhythmias, nausea, diarrhea, developed when using Amlodipine-KV, Amlodipine-Farmak and Amlodipine-Astrafarm (table 3).

SE to CA, which were recorded during the analysis of cards-notifications, coincide with the literature data [15–18]. As for amlodipine drugs, which received the largest number of reports of adverse reactions, one of the explanations may be that amlodipine drugs

are the leaders of the Ukrainian pharmaceutical market and world pharmaceutical market too. In addition, these drugs are the most demanded and popular among doctors and consumers [19, 20].

According to the data of 10 systematic reviews, the most common SE of CA are swelling of the lower extremities and reflex tachyarrhythmia [21, 22].

One of the ways to minimize the SE of amlodipine is to use its S-enantiomer. To achieve the optimal therapeutic effect of S-amlodipine, doses of the drug are two times smaller, which leads to fewer SE. The use of isolated S-amlodipine instead of the racemic mixture has many advantages because

Distribution of the number of side effects of the most commonly used calcium antagonists in Kharkiv and Kharkiv region for the period 2017–2021

Side effects	The number of registered side effects for 5 years					
	Amlodipine- Astra-farm	Amlodipine- KV	Amlodipine- Farmak	Amlodipine- Zdorovya	Amlodipin, Technolog	Ataline
Edemas of the lower extremities	23	25	29	13	4	18
Edemas of face	1		1			1
Tachyarrhythmia	1	4			3	3
Hypotension		1			2	
Rash on the skin	4	4	1	2	2	2
Itching of skin		2	1		1	
Angioedema	1	1	1	1		1
Headache	1	2				
Dizziness					1	
Insomnia		1				1
Tinnitus					1	
Paresthesias	1	1				2
Total number	32	41	33	16	14	28

the required dose and SE can be reduced [23, 24]. Another way to improve the effectiveness and safety of CA is the use of modern drugs of the latest generation. So, for example, – felodipine – one of the most effective antihypertensive agents in the treatment of hypertension. Its pharmacodynamics is characterized by a highly selective effect on precapillary resistance vessels, and the effect on vascular tissue is one hundred times stronger than on the myocardium [25, 26]. An important place in the therapy of hypertension is occupied by lercanidipine, the 3rd generation dihydropyridine derivative, which has a unique pharmacokinetics, is characterized by high lipophilicity and maximum vascular selectivity. It has been proven that

lercanidipine also exhibits nephroprotective properties, since, unlike other CA, the drug effect expands not only afferent but also efferent arterioles. Lercanidipine has high hypotensive activity in patients with chronic renal failure [27].

The next direction of increasing the safety of CA is complex pharmacotherapy. The use of combined drugs, which include components with different mechanisms of action, pharmacokinetics and pharmacodynamics, is one of the promising directions for the prevention of various complications in patients with hypertension [28, 29]. So, for example, in the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm) study, the combination of amlodipine

and perindopril proved to be particularly effective in patients with ischemic heart disease in combination with hypertension. In addition, both drugs are metabolically neutral. The effect of the combination on central aortic pressure indicates its particular effectiveness in situations with increased pulse pressure, for example, in the elderly. Also popular is the combination of CA with diuretics (for example, with hydrochlorothiazide, indapamide), which allows not only to avoid leg swelling, but also potentiates the antihypertensive effect of CA [30].

Conclusions

1. The range of calcium channel blockers on the modern pharmaceutical market of Ukraine is quite wide. Dihydropyridine derivatives predominate, namely, amlodipine drugs, pre-
 2. dominate among the registered medicines of this group. However, there are only 6 drugs of phenylalkylamine and benzothiazepine derivatives.
 3. The most common SE of CA are leg swelling and reflex tachyarrhythmia. These adverse reactions did not require additional hospitalization and did not cause disability of the patients.
 4. Three main directions for increasing the level of safety of CA have been established. The first is related to the use of stereoisomers. The second direction is the use of drugs of the latest generation. A promising direction is also CA combination with antihypertensive drugs of other pharmacological groups. The results obtained can be used by practicing doctors and health care organizers to optimize the pharmacotherapy of cardiovascular diseases.
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Конфлікт інтересів відсутній.

K. G. Shchokina, H. V. Belik, O. V. Tkachova, M. V. Savokhina
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According to the World Health Organization, the development of side effects (SE) of drugs is one of the serious medical problems. The relevance of this problem is proven by numerous statistical data obtained in different countries of the world.

The aim of the study – to analyze the SE of calcium antagonists (CA) in Kharkiv and Kharkiv region for the period of 2017–2021 and to provide recommendations for their minimizations, to conduct an analysis of the assortment on the Ukrainian pharmaceutical market, an analysis of the evidence base and clinical effectiveness of CA.

The work used methods of passive pharmacovigilance, namely the method of spontaneous reports, as well as the method of a systematic approach and systematic analysis. To analyze the clinical effectiveness

and conditions of rational use of calcium antagonists, well-known databases were used: Cochrane Library, Trip Database, and PubMed. These databases contain systematized primary or secondary information on a specific clinical issue: the effectiveness and safety of various medical technologies.

It was shown that the range of calcium channel blockers on the modern pharmaceutical market of Ukraine is quite wide. Dihydropyridine derivatives predominate, namely, amlodipine drugs, predominate among the registered medicines of this group. However, there are only 6 drugs of phenylalkylamine and benzothiazepine derivatives.

The results obtained of the conducted studies and data from the literature showed that the most frequent side effects of CA are edema of the lower extremities and reflex tachyarrhythmia. According to the analyzed results of systematic reviews, three main directions of increasing the safety level of CA have been established. The first is related to the use of stereoisomers. The second direction is the use of drugs of the latest generation. A promising direction is also the combination of CA with antihypertensive drugs of other pharmacological groups.

The results obtained can be used by practicing doctors and health care organizers to optimize the pharmacotherapy of cardiovascular diseases.

Key words: cardiovascular diseases, calcium antagonists, side effects, optimization of pharmacotherapy

К. Г. Щокіна, Г. В. Белік, О. В. Ткачова, М. В. Савохіна

Аналіз побічних ефектів антагоністів кальцію та визначення шляхів їхньої мінімізації

За даними Всесвітньої організації охорони здоров'я, розвиток побічної дії ліків є однією з серйозних медичних проблем. Актуальність цієї проблеми підтверджується численними статистичними даними, отриманими в різних країнах світу.

Мета дослідження – аналіз асортименту на фармацевтичному ринку препаратів групи антагоністів кальцію (АК), зареєстрованих в Україні, аналіз доказової бази щодо їхньої клінічної ефективності, а також аналіз побічних ефектів, що викликали АК, за допомогою карт повідомлень про побічні реакції в Харкові та Харківській області за період 2017–2021 років; надання рекомендацій щодо мінімізації побічних ефектів препаратів даної групи.

У роботі використовували методи пасивного фармаконагляду, а саме метод спонтанних повідомлень, також метод системного підходу та системного аналізу. Для аналізу клінічної ефективності та умов раціонального застосування АК використовували відомі бази даних доказової медицини: Cochrane Library, Trip Database, PubMed. Ці бази даних містять систематизовану первинну та вторинну інформацію з конкретної клінічної проблеми щодо ефективності та безпеки різних медичних технологій.

Показано, що спектр АК на сучасному фармацевтичному ринку України є доволі широким з домінуванням похідних дигідропіридину, зокрема препаратів амлодипіну.

Отримані результати проведених досліджень і дані літератури показали, що найчастішими побічними ефектами АК є набряк нижніх кінцівок і рефлекторна тахіаритмія. За проаналізованими результатами аналізу систематичних оглядів встановлено три основні напрями підвищення рівня безпеки АК. Перший рівень пов'язаний зі застосуванням стереоізомерів, другий – з використанням препаратів останнього покоління. Перспективним є також поєднання АК з антигіпертензивними препаратами інших фармакологічних груп.

Результати отриманих досліджень можуть бути використані лікарями-практиками й організаторами охорони здоров'я для оптимізації фармакотерапії серцево-судинних захворювань.

Ключові слова: серцево-судинні захворювання, антагоністи кальцію, побічні ефекти, оптимізація фармакотерапії

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