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ADVERSE REACTIONS OF ACE INHIBITORS. RETROSPECTIVE ANALYSIS OF SPONTANEOUS REPORTS IN LOCAL DATABASE

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Abstract

Among the diseases of the cardiovascular system, arterial hypertension due to the significant prevalence of the disease, a high risk of complications and low patient compliance takes a special place. One of the most important factors playing a role in the pathogenesis of hypertension is the activation of the renin-angiotensin-aldosterone system. Angiotensin-converting enzyme inhibitors are widely used in the treatment of hypertension. The aim of this work was to establish the clinical manifestations and frequency of adverse drug reactions associated with the use of angiotensin-converting enzyme inhibitors, and in second to study the severity and preventability of reactions.

A total of 128 reactions reports were registered in the Republic of Crimea in patients with diagnosed hypertension. They were recorded in the regional pharmacovigilance database. Most often the risk of adverse drug reactions was associated with the use of Enalapril (31.3%) and Lisinopril (24.2%). Among the combinations, the most frequent reactions recorded for Captopril and Hydrochlorothiazide (14.1%) and Enalapril and Hydrochlorothiazide (7%) combinations. Reactions were registered in people aged 51-60 years - 35.2% and 61-70 years - 26.4%. The occurrence of reactions in women was reported more often (71.9%) than in men (28.1%). In half of the cases, the main manifestations were disorders of the respiratory system (a dry cough) (48.4%). The frequency of angioedema was 11.7%, and in 5 cases patients had life-threatening laryngeal edema. There were reports about the lack of efficacy (11.7%). Polypharmacy was observed in 3.1% of cases. Analysis of the severity and preventability showed that the majority of reactions were mild and unavoidable. The number of drug-related problems was 4 per case.

The obtained results differ from the safety data for angiotensin-converting enzyme inhibitors got from clinical studies. It may be explained by the peculiarities of the chosen method and underreporting.

Keywords: *adverse reactions, angiotensin- converting enzyme (ACE) inhibitors, severity, preventability, pharmacovigilance*

Introduction

According to WHO information, cardiac and vascular disorders are the most serious problems in the world. Among other chronic diseases of the vascular system, arterial hypertension (AH) takes a special place. It is caused by the significant prevalence of the disease, the frequency of which in the Russian Federation exceeds 39%, a high risk of complications and low patient compliance [*Shalnova SA et al, 2006; Sinkova GM, 2007*]. According to the modern classification of AH of the European Society of Cardiology and the European Society of Hypertension, hypertension is diagnosed at a level of systolic and/or diastolic pressure equal to or higher than 140/90 *mm Hg*. Level of blood pressure should be based on the

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results of two or more blood pressure measurements [*Mancia G et al, 2007*].

One of the most important factors that play a role in the pathogenesis of AH is complex neurohumoral activation of the renin-angiotensin-aldosterone system (RAAS) [*Dzau VJ et al, 2006*]. Increased secretion of renin and other metabolites, in particular angiotensin II (AT-II) and aldosterone, leads to the development of hypertension, the damage to target organs, remodeling of the heart and blood vessels and other changes not directly related to increased blood pressure [*Romanenko VV, Romanenko ZV, 2014*].

There are three main pharmacological groups of drugs which may be prescribed to decrease the activity of the RAAS on the pharmaceutical market of the Russian Federation. One of these groups is the group of angiotensin-converting enzyme (ACE) inhibitors (ACEI), which history began after the research of Sergio Enrico Ferreira, who found in 1965 in the venom of the Southern American snake (*Bothrops jararaca*) an oligopeptide, which he called the "bradykinin-potentiating factor" [*Ferreira SH, 1965*] and researches of investigator groups from Squibb company, which in 1975 synthesized first peroral ACEI Captopril, authorized for medical use in 1981 [*Cushman DW, Ondetti MA, 1991; Smith CG, Vane JR, 2003; Erdös EG, 2006*]. Currently, there are more than a dozen of ACEI introduced into clinical practice.

It is worth to note that, since 1988, ACEI have consistently been among the first-line antihypertensive drugs in all international and national recommendations for the treatment of arterial hypertension [*The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, 1988; Dzhaiani NA, 2010; Banerji A et al, 2017*]. The compliance of ACEI with the requirements for modern antihypertensive drugs is caused not only by the ability of these drugs to ensure a persistent reduction in blood pressure and exert organoprotective action but also by the high safety profile of these drugs.

The aim of this work was to establish the main clinical manifestations and frequency of adverse drug reactions (ADR) associated with the administration of ACEI in patients with AH living in the Crimea Republic. A secondary aim of our work was to study the severity and preventability of found ADR, as well as the problems associated with drugs (Drug-related problems; DRP).

Material and methods

The objects of the study were ADR reports ("yellow cards") recorded in the regional database of spontaneous reports named "ARCADe" (Adverse Reactions in Crimea – the Autonomous Database) for the period from January 2010 to December 2016. A total of 128 reports about ADR of ACEI, prescribed for patients with the diagnosis of arterial hypertension (ICD code I10-I15), were analyzed.

The analysis was carried out taking into account the codes of the Anatomical and therapeutic classification (ATC) of medicinal products developed by WHO collaborating centre in Oslo, Norway.

To assess the severity of ADR caused by ACEI, the following methods were used: LDS scale [*Classen DC et al, 1997*], proposed by the University Hospital in Salt Lake City (USA), Karch-Lasagna method [*Talbot J, Aronson JK, 2011*] and Hartwig-Siegel criteria [*Hartwig SC et al, 1991; Talbot J, Aronson JK, 2011*]. According to these methods, reactions of mild, moderate and severe grade are distinguished, but the latter two methods separately distinguish lethal reactions (as the most severe grade). LDS method due to the scoring approach additionally allows a comparison of the severity of different ADR falling into one group. According to the number of LDS points, cases scored from 0 to 4 points are considered as mild reactions, ADR scored from 5 to 7 points as reactions of moderate severity, and from 8 points and more – as severe reactions. A similar approach is used in the Hartwig-Siegel methodology, but instead of scoring, the authors of the method proposed seven levels of ADR severity, and one one of them, the fourth, divided into two sublevels - 4A and 4B. Mild reactions have a level from 1 to 2, ADR of moderate severity have levels from 3 to 4B, and severe ones associated to level 5 or higher. It is important to note that the use of special terms related to the severity of ADR in the Russian medical literature is not unified; therefore, in this paper, we used the definitions given in the book "Stephens' Detection and Evaluation of Adverse Drug Reactions: Principles and Practice" [*Talbot J, Aronson JK, 2011*].

The assessment of ADR preventability was carried out using the following methods: Schumock

and Thornton criteria, Granada test, and Hallas criteria. According to the first two methods, there are avoidable and unavoidable ADR. The reaction is avoidable when researchers received a positive response to one or more criteria proposed by the authors of mentioned methods [*Schumock GT, Thornton JP, 1992*]. According to the Hallas criteria, ADR can be a definitely avoidable, possibly avoidable and unavoidable. Additionally, this method allows to distinguish an unclassifiable preventability, when there are not enough data to evaluate ADR or data are contradictory [*Hallas J et al, 1990*].

The analysis of drug-related problems (DRP) was carried out using the European qualification system DRP PCNE V5.01, which is based on coding in 4 sections: P - problems, C - causes, I - interventions and O - outcomes [*Eichenberger PM et al, 2010*]. The minimal amount of DRP is an indicator of the safe pharmacotherapy and accessible quality of life. High amount of DRP may indicate a high risk of potential complications when using the drug.

Results

For the analysis of ADR, we performed a search in ARCADe regional database of spontaneous reports with timeframes from 1 January of 2011 to 31 December of 2016 and found 128 records containing information about ADR caused by ACEI, therefore the frequency of them was 2.54% of the total number of records inputted during this period (5047 cases). It should be noted that the use of ACEI is one of the most frequent causes of ADR, second only to antibiotics and NSAIDs [*Konyaeva EI, Matveev AV, 2014*].

Further analysis was aimed at studying the main representatives of the ACEI, the use of which was associated with the development of undesirable consequences for the patient (Diag. 1). The results of the analysis showed that the risk of ADR was most often associated with the use of Enalapril (40 cases, 31.3% of total number of ACEI ADR) and Lisinopril (31 cases, 24.2%). Less commonly, ADR was caused by Perindopril (11 cases, 8.6%), Ramipril (5 cases, 3.9%), Captopril (3 cases, 2.3%), Quinapril and Fosinopril – (1 case for each, 0.8 %). It is worth to note, that the results also included cases of ADR resulted from using of a combination of antihypertensive drugs, which contain ACEI as one of the components. Among the combinations, most frequently ADR occurred when combinations of Captopril and Hydrochlorothiazide (18 cases, 14.1%), Enalapril and Hydrochlorothiazide (9 cases, 7%), and Perindopril and Amlodipine (3 cases, 2.3%) were prescribed. In rare cases, ADR was associated with the use of other combinations of antihypertensive drugs (Perindopril + Indapamide; Lisinopril + Amlodipine; Ramipril + Hydrochlorothiazide; Lisinopril + Hydrochlorothiazide, Enalapril + Indapamide) (Fig.1).

The distribution of records by patients` age yielded the following results: most of ACEI ADR were detected in individuals between the ages of 51 - 60 years (44 cases; 35.2%) and 61-70 years – (33 cases; 26.4%). It is comparable to an increase in the AH incidence in patients at these age periods and necessitates the use of antihypertensive drugs (Fig. 2).

The study of the influence of the gender on the incidence of events showed that ADR more fre-

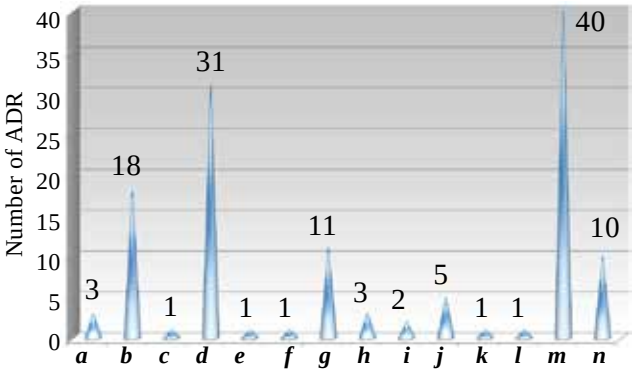

Figure 1. *The distribution of ACEI, according to their ATC codes and the frequency of ADR.*

Notes: ***a*** *– Captopril;* ***b*** *– Captopril and diuretics;* ***c*** *– Quinapril and diuretics;* ***d*** *– Lisinopril;* ***e*** *– Lisinopril and Calcium channel blockers;* ***f*** *- Lisinopril and diuretics; g – Perindopril;* ***h*** *– Perindopril and Amlodipine;* ***i*** *– Perindopril and diuretics;* ***j*** *- Ramipril;* ***k*** *– Ramipril and diuretics;* ***l*** *- Fosinopril;* ***m*** *- Enalapril;* ***n*** *– Enalapril and diuretics.*

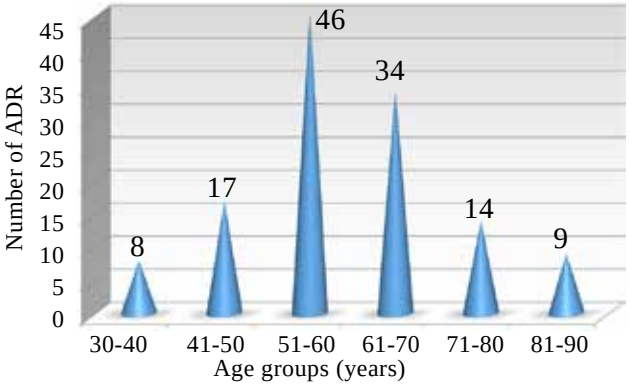

Figure 2. *Distribution of patients with manifestations of ACEI of adverse drug reactions by age (in years) of patients.*

quently occurred in females - 92 cases (71.9%), and much less frequently in males - 36 cases (28.1%).

The clinical manifestations of ADR that occur in patients taking ACEI revealed that in almost half of cases, the main manifestations were respiratory system disorders (a dry cough and tickle). The occurrence of such ADR was 48.4% (62 cases).

In 37 records (28.9%) we found the description of allergic reactions of varying severity (pruritus, petechiae, angioedema of the lips, eyelids and tongue). The number of cases of angioedema was 15 (11.7%), and in 5 cases (3.9%) patients had laryngeal angioedema, which required urgent hospitalization and emergency pharmacotherapy.

Disorders of the central nervous system (headache, insomnia, dizziness) and the cardiovascular system (tachycardia, edema of the lower extremities) were observed with the same frequency - in 3.9% of cases (5 cases each).

Particular attention is paid to the high incidence (15 cases; 11.7%) of the lack of antihypertensive effect, which may constitute a threat to the QoL and health of patients and requires mandatory replacement of the drug or correction of its dose. All clinical manifestations of ACEI ADR are presented in figure 3.

Further study of the reports showed that drug correction to relieve the clinical manifestations of adverse reactions was needed in 50 cases (39.1%), and in the remaining 78 cases (60.9%) ADR did not require additional pharmacotherapy.

The consequences of reactions in patients taking ACEI as part of antihypertensive therapy had the following features: life-threatening conditions in the form of angioedema were observed in 5 cases, the development of temporary disability in 8 cases, and the need for hospitalization occurred in 4 patients. In the remaining 111 cases (86.7%), the ADR were not serious and did not cause any consequences.

Particular attention was paid to the study of the number of drugs simultaneously prescribed with ACEI, which is important in determining the causal relationship between the fact of taking the medicine and the emerging ADR. The results of the analysis of the yellow cards showed that in 52 cases (40.6%), ACEI were used as monotherapy. In 39 cases (30.5%) there was a simultaneous prescription of the ACE inhibitor group and one concomitant drug, in 15 and 18 cases there was a simultaneous prescription of two and three concomitant drugs, respectively (Fig. 4). The phenomenon of polypharmacy (simultaneous administration of 5 or more drugs) was observed in 4 cases (3.1%).

Further analysis was aimed at studying the severity and preventability of ADR arising from the use of drugs belonging to the ACEI group. Studying the severity of ACEI reactions with the LDS scale showed that mild grade of ADR were most common - 114 cases (89.1%), moderate and severe ADR were much less common - in 8 and 6 cases, respectively (Fig. 5).

The results of applying the Karch-Lasagna method for assessing the severity showed the following results: minor (mild) ADR were observed in 74 cases (57.8%), reactions were moderate in 49 cases (38.3%) and severe ones occurred in 5 cases (3.9%). There were no cases of the development of lethal ADR.

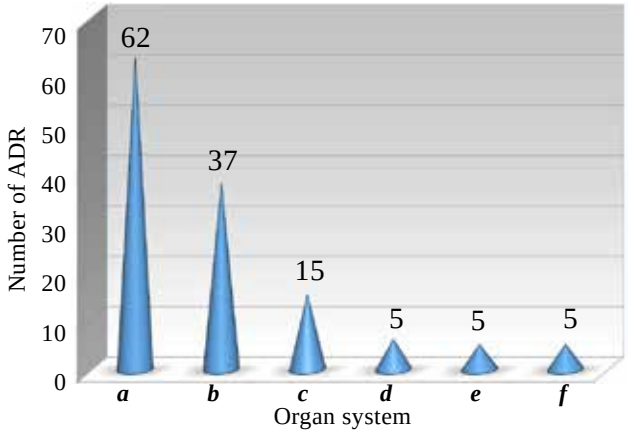

Figure 3. *Clinical manifestations of ACEI ADR according to the type of the affected system.*
Notes: ***a*** *- Respiratory System,* ***b*** *- Allergic Sindrome,* ***c*** *– No effect,* ***d*** *- Cardiovascular System,* ***e*** *- Central Nervous System,* ***f*** *- Gastrointestinal System,*

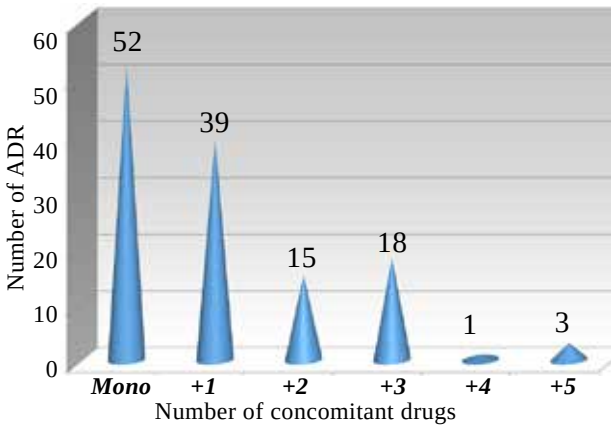

Figure 4. *Analysis of ADR reports by the number of concomitant drugs.*

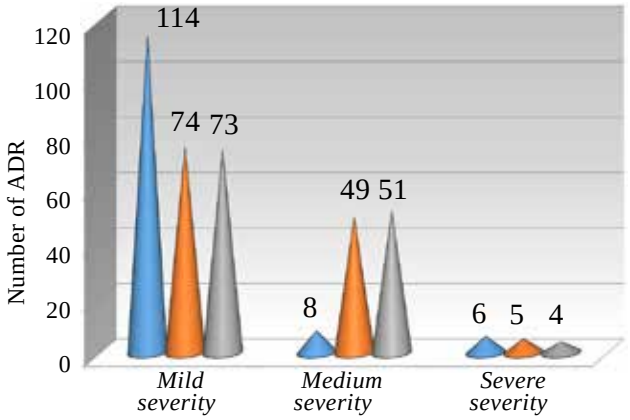

Figure 5. *The results of the analysis of the ACEI ADR severity, assessed by the LDS scale (left pyramids), Karch-Lasagna (middle pyramids) and Hartwig-Siegel (right pyramids) methods*

Determination of the severity in accordance with the criteria of Hartwig-Siegel made it possible to estimate that in 73 (57%) cases observed ADR had mild severity, in 51 cases (39.8%) - moderate severity and in 4 cases (3.1%) – they were severe, this was comparable with the results calculated by the Karch-Lasagna method.

At the next stage of the analysis, the preventability of drug reactions was studied. The assessment of preventability in accordance with the Schumock and Thornton criteria showed that 16 cases of ACEI ADR (12.5%) could be considered as "possibly preventable", in the remaining cases the ADR were unavoidable. The application of the Hallas criteria showed that all cases of ADR were unavoidable Using the Granada test revealed 6 cases (4.7%) when ADR were classified as "possibly preventable", and the remaining 122 as "unavoidable" (Fig 6).

At the conclusion of our analysis, for each of the presented INNs, we estimated the number of DRP (drug related problems - drug-related problems). This method has shown that ACEI do not cause any particular problems with use. The average number of DRPs (median) was 4 per one case, with the greatest number of problems found in the Lisinopril group and the group of a combination of Captopril and Diuretics (n=5). In one case 12 DRPs were noted (Captopril plus Hydrochlorothiazide). The minimal number of problems was noted in the Captopril monotherapy group (n=3). No any statistically significant differences were found (T Kruskal-Wallis = 18.03; P = 0.1563) between ACEI INN.

Discussion

ACE inhibitors, despite their 40-year history of the use in medical practice, are still in demand among doctors and patients. Their effectiveness is beyond doubt, since has been demonstrated by numerous high-quality clinical studies and confirmed in meta-analyses [*Romanenko VV, Romanenko ZV, 2014*]. Indications for use of ACEI are expanding and are no longer limited only to AH. Currently, they are recommended for patients with IHD, CHF and chronic renal failure [*Dzhaiani NA, 2010*].

However, along with the effectiveness of ACEI therapy, their safety is of considerable importance. The study of ADR in clinical trials is important, but more and more specialists are paying attention to real clinical data obtained in the process of post-registration use (RWE – real-world evidence), such as data from registries, databases, observational studies, individual clinical cases and case series. That is why the data of 128 cases from our database may be of interest for general practitioners, cardiologists, clinical pharmacologists, as well as for health care managers, pharmacovigilance specialists in pharma companies and regulatory agencies.

The proportion of ACEI ADR spontaneous reports from doctors in the Crimea region ranged from 5.8% in 2010 to 2.7% in 2016. This is consistent with the data of other authors who analyzed the pharmacovigilance databases. Dubrall et al. analyzed the German pharmacovigilance data from 1978 to 2016, and the frequency of ACEI ADR was 3.7% of all reports (Total number of cases was

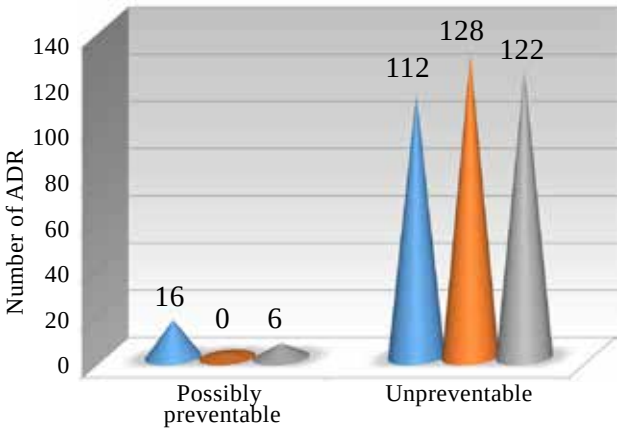

Figure 6. *The results of the preventability study of ACEI ADR, assessed by the Schumock and Thornton method (left pyramids), Hallas criteria (middle pyramids) and the Granada test(right pyramids).*

345,662) [*Dubrall D et al., 2018.*]. The number of submitted reports depends on the activity and intensity of the pharmacovigilance work and the doctors' alertness regarding ADR, both serious and unserious. In the study of Fang et al. the frequency of ACEI ADR was 0.9% [*Fang H et al., 2017*], but after the introduction into practice of methods aimed at improving the serious ADR reporting, not a single message was registered.

Data about leading clinical manifestations of ADR is always of particular interest. In our study, the main manifestation was a cough (62 cases, 48.4%), which is caused by an increase in bradykinin level [*Dancev IC et al, 2015*]. It should be noted that this is significantly higher than the frequency of cough in the study of Wood and colleagues. (12.3%) [*Wood R, 1995*], the above-mentioned large-scale study of Dubrall et al. [*Dubrall D et al., 2018*] (7%), Indian trials performed by Trivedi et al. (10.7%) [*Trivedi MD et al, 2017]* and Mahmoudpour et al. (14.4%) [*Mahmoudpour SH et al, 2015*], in the results of the analysis of 134,985 database records of patients taking ACEI (5.3%) [*Banerji A et al, 2017*], and other studies. It is noteworthy that the closest for our results finding of the cough frequency (44%) were noted by Chinese authors [*Woo KS, Nicholls MG, 1995*].

The incidence of ACEI-induced angioedema, in the pathogenesis of which a high level of bradykinin also plays a leading role, was 11.7% in our region, while in the study of Trivedi and colleagues it was significantly less - 0.6% [*Trivedi MD et al, 2017*], as in retrospective cohort studies of G. Burkhart and S. Toh [*Burkhart GA et al, 1996; Toh S et al,2012*] (0.2% and 0.4%, respectively). A lower frequency of angioedema was also found in the analysis of 12 RCTs conducted by Mancia and Schumacher - 0.2% [*Mancia G, Schumacher H, 2012*], Systematic review of 26 RCT of Makani et al. - 0.5% [*Makani H et al, 2012*], and analysis of 13,4855 electronic records conducted by a group of experts from Boston (0.7%) [*Banerji A et al, 2017*]. On the contrary, in the already mentioned ADR national database of Germany the frequency of angioedema was significantly higher and reached 9% [*Dubrall D et al, 2018*], which is more close to our results.

In our opinion, such differences between the data are explained by the peculiarities of the spontaneous reporting method in the post-registration period. Due to the lack of reports about ADR, identifying of which requires additional research that may not be mandatory in outpatient practice, the proportion of reports, which are more severe and cause concern to the doctor and patient (such as cough or angioedema), is increasing. In this regard, attention is drawn to the fact that there are no reports about the development of hyperkalemia, hypotension, kidney damage, proteinuria, anemia, etc. from the Crimean doctors. This is clear from the point of view of the chosen method (analysis of spontaneous reports), which is characterized by the prevalence of type B reactions [*Logvinovskaya OA et al, 2017*], as well as the presence of a well-known problem called underreporting [*Hazell L, Shakir SA, 2006; Tandon VR et al, 2015*].

A sufficiently high percentage of reports about the lack of effectiveness also requires attention. The expediency of ACEI administration in the therapy of AH is beyond doubt, therefore these records, with the proper quality of the used drugs, should be interpreted as a sign of insufficient therapy in patients with an uncontrolled course of the disease. We assume that in this group of patients, the prime cause of the lack of effectiveness was the incorrect choice of antihypertensive drugs and/or the incorrect determination of the severity of hypertension. Unfortunately, the format of the reports and the design of our research does not allow us to determine the correctness of such assertion, which undoubtedly is the limitation of this study.

A small number of records with detected polypharmacy, which we interpreted as prescribing of five or more drugs to one patient at the same time [*Sychev DA et al, 2016*], may indicate proper compliance by doctors with national guidelines for the treatment of hypertension, which implies a clear approach to the choice of antihypertensive drugs and their combinations. This conclusion is supported by the high percentage of detected unavoidable ADR, assessed by three independent methods.

The rare development of severe ADR also indicates the safety of the ACEI group. This result was demonstrated by three different methods too.

Unfortunately, we were unable to find publications with the results of studies of the severity and preventability of ACEI ADR by at least one of the methods we choose. Satisfactory agreement of

methods to assess the severity and preventability was shown in previous works of our team [*Petrov AV et al, 2018; Matvieiev O et al, 2014*] and comparisons with data from other research groups would confirm our assumptions. Future studies of this problem (the safety of ACEI), in our opinion, should necessarily include such assessments.

CONCLUSION

1. The results of the study of ADR, caused by ACEI in Crimean patients with AH showed that the most frequently the development of reaction was associated with the use of Enalapril and Lisinopril, as well as of combination of drugs containing Captopril and diuretic (Hydrochlorothiazide).
2. Among the main manifestations of ACEI ADR, it is necessary to highlight the disturbances of the respiratory system (a dry cough) and angioedema.
3. The data on the ADR frequency, obtained as a result of the analysis of spontaneous reports, significantly differs from the information about the safety of ACEI inhibitors found in clinical trials and systematic reviews.
4. Study of the severity and preventability showed that the majority of reported reactions were unavoidable events with mild or moderate severity.
5. Future studies of the ACEI safety should include an assessment of the severity and preventability of ADR.

REFERENCES

1. *Banerji A, Blumenthal KG, Lai KH., et al.* Epidemiology of ACE Inhibitor Angioedema Utilizing a Large Electronic Health Record. J Allergy Clin Immunol Pract. 2017; 5(3): 744-749.
2. *Burkhart GA, Brown NJ, Griffin MR., et al.* Angiotensin converting enzyme inhibitor-associated angioedema: higher risk in blacks than whites. Pharmacoepidemiol Drug Saf. 1996; 5: 149-154.
3. *Classen DC, Pestotnik SL, Evans RS., et al.* Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1997; 277: 301-306.
4. *Cushman DW, Ondetti MA.* History of the design of captopril and related inhibitors of angiotensin converting enzyme. Hypertension. 1991; 17; 589-592.
5. *Dancev IS, Sinicina II, Sychyov DA.* [Cough and angioedema against the background of taking angiotensin-converting enzyme inhibitors: genetic markers] [Published in Russian]. Pharmacogenetics and Pharmacogenomics. 2015; 2: 9-13.
6. *Dubrall D, Schmid M, Alešik E., et al.* Adverse Drug Reactions, and Medication Groups under Suspicion. Dtsch Arztebl Int. 2018; 115(23): 393-400.
7. *Dzau VJ, Antman EM, Black HR., et al.* The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part I: Pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). Circulation. 2006; 114(25): 2850-2870.
8. *Dzhaiani NA.* [Some aspects of the use of lisinopril in hypertension] [Published in Russian]. Rational pharmacotherapy in cardiology. 2010; 6(1): 95-102.
9. *Eichenberger PM.* Classification of drug-related problems with new prescriptions using a modified PCNE classification system. Pharmacy World & Science. 2010; 3(32): 362-372.
10. *Erdös EG.* The ACE and I: how ACE inhibitors came to be. The FASEB Journal 2006; 20: 1034-1038
11. *Fang H, Lin X, Zhang J., et al.* Multifaceted interventions for improving spontaneous reporting of adverse drug reactions in a general hospital in China. BMC Pharmacol Toxicol. 2017; 18(1): 49.
12. *Ferreira SH.* A bradykinin-potentianting factor (BPF) present in the venom of bothrops jararaca. Brit J Pharmacol. 1965; 24: 163-169.
13. *Hallas J, Harvard B, Gram LF et al.* Drug related hospitaladmissions: the role of definitions and intensity of data collection, and the possibility of prevention. Intern Med. 1990; 228 (2): 83-90.
14. *Hartwig SC, Denger SD, Schneider PJ.* Severity-indexed, incident report-based medication error-reporting program. Am J Hosp Pharm. 1991; 48: 2611-2616.
15. *Hazell L, Shakir SA* Under reporting of adverse drug reactions: a systematic review. Drug Saf. 2006; 29(5): 385-396.

16. *Konyaeva EI, Matveev AV.* [Adverse drug reaction of medicine in the Republic of Crimea in 2013] [Published in Russian]. Safety and risk of pharmacotherapy. 2014; 3(4): 20-26.

17. *Logvinovskaya OA, Romanov BK, Kolbin A.S., et al.* [Methods of working with signals in pharmacovigilance] [Published in Russian]. Quality Clinical Practice. 2017; 3: 38-42.

18. *Mahmoudpour SH, Asselbergs FW, de Keyser CE., et al.* Change in prescription pattern as a potential marker for adverse drug reactions of angiotensin converting enzyme inhibitors. Int J Clin Pharm. 2015; 37(6): 1095-1103.

19. *Makani H, Messerli FH, Romero J., et al.* Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. Am J Cardiol. 2012; 110: 383-391.

20. *Mancia G, Backer de G, Dominiczak A., et al.* 2007 Guidelines for the mangement of arterial hypertension. Europan Heart J. 2007; 28: 1462-1536.

21. *Mancia G, Schumacher H.* Incidence of adverse events with telmisartan compared with ACE inhibitors: evidence from a pooled analysis of clinical trials. Patient Prefer Adherence. 2012; 6: 1-9.

22. *Petrov AV, Matveev AV, Krasheninnikov AE., et al.* [Analysis of required reactions against the background of obtaining nonsteroides and prevention preparations by communications obtained in 2011-2016 in the Republic of Crimea] [Published in Russian]. Effective pharmacotherapy. 2018; 4: 6-9.

23. Polyparmacy in clinical practice: the problem and solutions. Under total. ed. D. A. Sychev. - St. Petersburg: CSC "Profession". 2016. 224p.

24. *Romanenko VV, Romanenko ZV.* [ACE inhibitors - first-line drugs in the treatment of cardiovascular diseases] [Published in Russian]. International Reviews. Clinical practice and health. 2014; 3: 5-25.

25. *Schumock GT, Thornton JP.* Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992; 27(6): 538.

26. *Shal'nova SA, Balanova YuA, Konstantinov VV., et al.* [Hypertension: prevalence, awareness, antihypertensive drugs and treatment efficacy among the population of the Russian Federation] [Published in Russian]. Russian Journal of Cardiology. 2006; 4: 45-50.

27. *Sin'kova GM.* [Epidemiology of arterial hypertension] [Published in Russian]. Siberian Medical Journal. 2007; 8: 5-10.

28. *Smith CG, Vane JR.* The discovery of captopril. The FASEB Jounal 2003; 17: 788-789.

29. *Talbot J, Aronson JK.* Stephens' Detection and Evaluation of Adverse Drug Reactions: Principles and Practice 2011. John Wiley & Sons, Ltd. p. 732.

30. *Tandon VR, Mahajan V, Khajuria V, Gillani Z.* Under-reporting of adverse drug reactions: a challenge for pharmacovigilance in India. Indian J Pharmacol. 2015; 47(1): 65-71.

31. *The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.* Arch Intern Med. 1988; 148(5): 1023-1038.

32. *Toh S, Reichman ME, Houstoun M., et al.* Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system Arch Intern Med. 2012; 172: 1582-1589.

33. *Trivedi MD et al.* Pharmacovigilance study of angiotensin-converting enzyme inhibitors in patients visiting Department of Medicine of a Tertiary Care Hospital, Surendranagar, Gujarat. International Journal of Basic & Clinical Pharmacology. 2017; 5: 870-873.

34. *Trivedi MD., et al.* Pharmacovigilance study of angiotensin-converting enzyme inhibitors in patients visiting Department of Medicine of a Tertiary Care Hospital, Surendranagar, Gujarat. International Journal of Basic & Clinical Pharmacology. 2017; 5: 870-873.

35. *Woo KS, Nicholls MG.* High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. Br J Clin Pharmacol. 1995; 40(2): 141-144.

36. *Wood R.* Bronchospasm and cough as adverse reactions to the ACE inhibitors captopril, enalapril and lisinopril. A controlled retrospective cohort study. Br J Clin Pharmacol. 1995; 39(3): 265-270.