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Angioedema induced by angiotensin-converting enzyme inhibitors: an analysis of hospitalizations during the COVID-19 pandemic



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ABSTRACT

BACKGROUND: The pathogenesis of angioedema induced by angiotensin-converting enzyme inhibitors is based on the accumulation of bradykinin as a result of angiotensin-converting enzyme blockade. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the angiotensin-converting enzyme 2 receptor, which may inhibit its production and thereby lead to an increase in bradykinin levels. Thus, SARS-CoV-2 infection may be a likely trigger for the development of angioedema. **AIMS:** This study aimed to analyze cases of hospitalizations of patients with angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers during the coronavirus disease 2019 (COVID-19) pandemic.

MATERIALS AND METHODS: This study retrospectively analyzed medical records of patients admitted to the Vitebsk Regional Clinical Hospital between May 2020 and December 2020 with isolated (without urticaria) angioedema while receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In all patients, smears from the naso- and oropharynx for COVID-19 were analyzed by polymerase chain reaction.

RESULTS: Fifteen inpatients (9 men and 6 women) aged 44–72 years were admitted because of emergent events, of which 53.6% had isolated angioedema. In two cases, a concomitant diagnosis of mild COVID-19 infection was established with predominant symptoms of angioedema, including edema localized in the face, tongue, sublingual area, and soft palate. All patients had favorable disease outcomes.

CONCLUSIONS: Patients with angiotensin-converting enzyme inhibitor-induced angioedema may require hospitalization to monitor upper respiratory tract patency. There were cases of a combination of angiotensin-converting enzyme inhibitor-induced angioedema and mild COVID-19. Issues requiring additional research include the effect of SARS-CoV-2 infection on the levels of bradykinin and its metabolites, the triggering role of COVID-19 in the development of angioedema in patients receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, recommendations for the management of patients with angiotensin-converting enzyme inhibitor-induced angioedema, and a positive result for COVID-19.

Keywords: angioedema; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; bradykinin; COVID-19

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Ангиоотёки, индуцированные ингибиторами ангиотензинпревращающего фермента: анализ госпитализаций в период пандемии COVID-19

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АННОТАЦИЯ

ОБОСНОВАНИЕ. В основе патогенеза ангиоотёков, индуцированных приёмом ингибиторов ангиотензинпревращающего фермента, лежит накопление брадикинина в результате блокады ангиотензинпревращающего фермента. Вирус SARS-CoV-2, связываясь с рецептором ангиотензинпревращающего фермента 2, возможно, подавляет его продукцию, что в свою очередь ведёт к повышению уровня брадикинина. Таким образом, инфицирование SARS-CoV-2 может являться вероятным триггером развития ангиоотёка.

ЦЕЛЬ — анализ случаев госпитализаций пациентов с ангиоотёками, ассоциированными с приёмом ингибиторов ангиотензинпревращающего фермента и блокаторов ангиотензиновых рецепторов в период пандемии COVID-19.

МАТЕРИАЛ И МЕТОДЫ. Проведён ретроспективный анализ медицинских карт стационарных пациентов, госпитализированных в Витебскую областную клиническую больницу в мае-декабре 2020 года с изолированными (без крапивницы) ангиоотёками на фоне приёма ингибиторов ангиотензинпревращающего фермента или блокаторов ангиотензиновых рецепторов. Всем пациентам были взяты мазки из носо- и ротоглотки на COVID-19 методом полимеразной цепной реакции.

РЕЗУЛЬТАТЫ. По экстренным показаниям госпитализировано 15 пациентов (9 мужчин и 6 женщин) в возрасте 44–72 лет, что составило 53,6% всех пациентов с изолированными ангиоотёками. В двух случаях установлен сопутствующий диагноз инфекции COVID-19 лёгкого течения с преобладанием в клинической картине симптомов ангиоотёка с локализацией в области лица, языка, подъязычной области, мягкого нёба. Все пациенты имели благоприятный исход заболевания.

ЗАКЛЮЧЕНИЕ. Пациенты с ангиоотёками, индуцированными ингибиторами ангиотензинпревращающего фермента, могут нуждаться в госпитализации с целью мониторинга проходимости верхних дыхательных путей. Выявлены случаи сочетания ангиоотёка на фоне приёма ингибиторов ангиотензинпревращающего фермента и инфекции COVID-19 лёгкого течения. Вопросы, требующие дополнительных исследований: влияние инфицирования SARS-CoV-2 на уровни брадикинина и его метаболитов; триггерная роль инфекции COVID-19 в развитии ангиоотёков у пациентов, получающих ингибиторы ангиотензинпревращающего фермента/блокаторы ангиотензиновых рецепторов; рекомендации по ведению пациентов с ангиоотёками, индуцированными ингибиторами ангиотензинпревращающего фермента, и положительным результатом на COVID-19.

Ключевые слова: ангиоотёк; ингибиторы ангиотензинпревращающего фермента; блокаторы ангиотензиновых рецепторов; брадикинин; COVID-19

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Abbreviations

AE — angioedema
ACE2 — angiotensin-converting enzyme 2
AT — angiotensin
ARB — angiotensin receptor blockers
BK — bradykinin

ACEi — angiotensin-converting enzyme inhibitors
HAE — hereditary angioedema
PCR — polymerase chain reaction
RAAS — renin-angiotensin-aldosterone system

Background

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) rank high in treating arterial hypertension and chronic heart failure. In addition, they are used to preserve renal function in patients with diabetes mellitus and chronic kidney disease. About 40 million people worldwide use ACE inhibitors, and the widespread use of this group of drugs has led to an increase in the prevalence of adverse drug reactions [1, 2].

Angioedema (AE) can generate potential life-threatening side effects in 0.1–0.7% of individuals receiving ACE inhibitors and somewhat less frequently while taking ARBs (0.1%) [3]. Among all cases of AE requiring hospitalization in the emergency department, the proportion of ACEi-induced AE is 30–40% [4, 5]. According to

our data, 44.8% of patients (total patients = 87) of the Vitebsk Regional Clinical Hospital were hospitalized for emergency indications with isolated AE in 2012 and had the reaction caused by the intake of ACE inhibitors [6]. Among patients seeking emergency care, up to 16% of patients required intubation, and 1% needed a tracheostomy. Rapid onset of symptoms, involvement of the tongue, soft palate or larynx, symptoms of salivation, and respiratory distress are associated with a higher risk of intubation [7].

AE caused by ACE inhibitors belongs to acquired bradykinin-mediated AE, and the vasodilating peptide bradykinin (BK) plays a key role in their pathogenesis. ACE inhibitors provide a decrease in the formation of angiotensin (AT) II and prevent the conversion of BK

into inactive metabolites, leading to its accumulation [8]. BK is also expected to participate in the development of AE when taking ARB [9, 10]. Thus, according to experimental data, one of the consequences of the blockade of AT1 receptors is a reactive increase in AT-II formation. The effect of AT-II on AT2 receptors leads to an increase in the BK level [9].

New drugs are being introduced into clinical practice that affect the renin-angiotensin-aldosterone system (RAAS) and can affect the BK metabolism, in particular, the neprilysin inhibitor sacubitril (used in fixed combination with valsartan), hypoglycemic drugs of the class of dipeptidyl peptidase 4 inhibitors (DPP4) [11]. BK is a nonapeptide that is cleaved from high molecular weight kininogen by plasma kininogenase. Its biological effect is implemented by activating B2 receptors located in the membranes of endothelial and smooth muscle cells. The resulting BK is rapidly inactivated by enzymatic degradation, mainly under the action of kininase II (ACE), as well as neutral endopeptidase (neprilysin) and DPP4. In addition, Carboxypeptidase N (kininase I) and aminopeptidase P (APP) catabolizes BK, forming partially active products. Angiotensin-converting enzyme 2 (ACE2) is involved in the cleavage of the BK active metabolite des-Arg9-bradykinin [2, 5]. It has also been revealed that polymorphism of genes encoding the corresponding molecules involved in the metabolism and action of BK (APP, DPP4, B2 receptor, etc.) may play a role in the development of AE when taking an ACE inhibitor. An elevated local level of BK leads to increased release of nitric oxide and prostaglandins. This enhances the vascular permeability in the postcapillary and venular regions with extravasation of fluid and the development of edema [2].

ACEi-induced AEs are pale, not itchy, not accompanied by urticaria, and are often localized in the region of the lips, tongue, pharynx, and larynx. The rare localization of AE also includes the abdominal organs. Edema can develop at different times from the beginning of the use of ACE inhibitors. Risk factors include African American origin, female gender, old age, smoking, and seasonal allergies. AE can resolve spontaneously. However, the continued use of ACE inhibitors can cause a relapse [5, 11]. After discontinuation of ACE inhibitors, the probability of AE recurrence remains approximately for 6 weeks by suppressing the tissue ACE. During this period, prescription drugs that reduce the RAAS activity to patients are not recommended [11]. In patients with ACEi-induced AE, the risk of such an adverse reaction when substituted for ARB is lower than 10% (0 – 17%) [12].

Patients with ACEi-induced AE require timely diagnostics and emergency care with correction of therapy to prevent recurrent episodes. The diagnosis is established based on anamnesis, clinical presentation, ruling out of histamine, and other types of bradykinin AE [5]. In the case of suspected AE caused by the intake of ACEi/ARB, these classes of drugs should be immediately stopped and, if necessary, replaced by drugs of other

pharmacological groups. After discontinuation of ACE inhibitors/ARB, edema usually resolves spontaneously within 48–72 hours [2]. Patients with AE localization on the face, neck, tongue, and larynx must be examined by an otorhinolaryngologist to assess the patency of the glottis and upper respiratory tract. The signs of obstruction such as inability to swallow, salivation, stridor, cyanosis, accessory muscle involvement in breathing, nasotracheal intubation or tracheotomy/conicotomy should also be examined promptly. Patients with AE of the tongue and larynx require follow-up in the intensive care unit [2, 13].

Standard treatment for the relief of AE caused by mast cell mediators includes administering antihistamines, systemic glucocorticoids, and, in severe cases, epinephrine. However, with ACEi-induced AE, this therapy is not pathogenetically justified and might be ineffective [14]. In this regard, to relieve AE caused by the intake of ACE inhibitors, a therapy aimed at BK, approved for the treatment of acute attacks of hereditary AE (HAE) was proposed. The therapy includes a blocker of BK type 2 receptors icatibant, an inhibitor of human C1-esterase, and fresh frozen plasma. Currently, the advantages of this approach in the treatment of ACEi-induced AE are insufficiently proven and require further investigations [2]. In a randomized controlled trial, M. Baş et al. [15] showed a faster resolution of the symptoms of ACEi-induced AE when using icatibant compared with standard therapy with prednisolone and clemastine. However, the efficacy of icatibant has not been confirmed in two other randomized trials evaluating its effect compared with placebo [16, 17]. In the occurrence of AE in patients receiving an ACE inhibitor (especially for a long time), various triggers are of great importance. Among the drugs that can contribute to the development of AE during the intake of ACE inhibitors, nonsteroidal anti-inflammatory drugs, calcium antagonists, DPP4 inhibitors, mTOR inhibitors (mammalian target of rapamycin), and other immunosuppressants are indicated.

Trauma, surgical manipulations in the head or neck area can be a provoking factor [2, 5, 8]. It is assumed that COVID-19 infection may also trigger the development of AE in patients receiving ACE inhibitors [18]. The SARS-CoV-2 virus, by binding to the ACE2 receptor, possibly suppresses the production of ACE2, which in turn leads to an increase in the BK level [19]. Cases of isolated AE have been described in patients infected with SARS-CoV-2 and receiving ACE inhibitors [18, 20, 21].

The work aimed to analyze the cases of hospitalizations of patients with AE associated with the intake of an ACE inhibitor or ARB during the COVID-19 pandemic.

Materials and methods

Study design

An observational single-center retrospective continuous controlled study was conducted, which included a comparative analysis of the medical records of patients

hospitalized during the COVID-19 pandemic with AE caused by the intake of ACE inhibitors/ARB, with cases of isolated AE from other causes.

Inclusion criteria

The inclusion criteria were an established diagnosis of AE.

Exclusion criteria were a combination of AE and urticaria, established diagnosis of HAE; family history of a confirmed diagnosis of HAE.

Conditions of conducting

The study was conducted in the Vitebsk Regional Clinical Hospital (VRCH, Republic of Belarus). During the study period, the patients aged 18 years and older with emergency allergic pathology were hospitalized at the VRCH.

Study duration

The enrollment period of the study was from May to December 2020. Therefore, there was no offset of the scheduled timeslots.

Description of the medical intervention

The study was performed using a continuous sample of medical records of patients treated in intensive care units and allergy departments of the Vitebsk Regional Clinical Hospital with isolated (without urticaria) AE from May to December 2020. Upon admission to the hospital, all patients underwent a mandatory laboratory study of biomaterial (nasopharyngeal and oropharyngeal swabs) for the presence of concomitant COVID-19 infection using the real-time polymerase chain reaction (RT-PCR) method. For further analysis, the study group included medical records of patients who received ACE inhibitors/ARB and did not have other obvious causes of the development of AE. The Naranjo algorithm was used to establish a causal relationship between the development of AE and the use of ACE inhibitors/ARB [22]. The control group included patients with isolated AE but not associated with the intake of an ACE inhibitor/ARB.

Main study outcome

Clinical and anamnestic data and laboratory and instrumental examinations of AE patients while taking ACE inhibitors/ARB were evaluated.

Additional study outcomes

Causative ACE inhibitors and ARB were analyzed.

Subgroup analysis

Hospitalized patients with isolated AE were distributed into two groups: patients with an ACEi/ARB-induced AE and a comparison group consisting of patients with AE but not associated with the intake of ACE inhibitors/ARB.

Outcome registration methods

Analysis of indicators entered into the database from medical records of hospital patients included de-

mographic indicators (gender, age); the main clinical diagnosis and concomitant diseases; AE localization; hospitalization in the intensive care unit; causative ACE inhibitors/ARB and concomitant medications; anamnestic data (episodes of AE, history of atopy, family history of AE); data of basic laboratory (complete blood count, biochemical blood test, coagulogram) and instrumental (chest X-ray, electrocardiogram) studies; the results of a qualitative determination of IgG/IgM to SARS-CoV-2 in blood serum and swabs from the nasopharynx and oropharynx for COVID-19 by PCR.

Ethical considerations

The Committee approved the study design on the Ethics of Clinical Trials of the Vitebsk State Order of Friendship of Peoples Medical University, protocol No. 7 dated 02.12.2020.

Statistical analysis

Principles for calculating the sample size. The sample size was not pre-calculated.

Statistical data analysis methods included Statistica 10.0 software (StatSoft Inc., USA) and Microsoft Office Excel 2016 (Microsoft Corporation, USA) for data processing. The median (25–75% interquartile range) of the patients' age was calculated as Me (25; 75); the Mann–Whitney test determined the significance of differences in quantitative indicators. The two-tailed Fisher's exact test determined the frequency of qualitative features. The results were considered to be statistically significant at $p < 0.05$.

Results

Objects (participants) of the study

In the study, we retrospectively assessed the medical records of 28 patients hospitalized for emergency indications at the VRCH from May to December 2020 with isolated AE. The group of patients with ACEi/ARB-induced AE included 15 patients (9 men and 6 women) who received treatment with ACE inhibitors/ARB and had no other obvious causes of the development of AE. The share of AEs caused by intake of ACEi/ARB was 53.6%. According to the Naranjo algorithm, a causal relationship with the intake of ACE inhibitors/ARB was determined as probable in 12 patients (80%) and as possible in 3 patients (20%). The patients were 44–72 years old; Me 59 (55; 62) years old. The comparison group included 13 patients (6 men and 7 women) aged 19–72 years; 47 (34; 62) years old. The difference in age with the ACEi/ARB-induced AE group was statistically insignificant ($p = 0.19$). Thus, in the comparison group, AE was caused by drugs in 4 out of 13 cases, by food in 1 out of 13 cases; and in 8 out of 13 patients, the cause of AE has not been established.

Key research findings

The characteristics of patients with ACEi/ARB-induced AE are presented in Table 1.

The localization of edema was noted in the face, tongue, and soft palate (Fig. 1). Peripheral AE was not found either in the study group or in the comparison group. The frequency of admissions to the intensive care unit of AE patients while taking an ACEi/ARB was 20% (3/15) and did not differ significantly from the group of patients with isolated AE, not associated with intake of an ACEi/ARB (4/13); $p = 0.67$. In the study group, repeated episodes of AE were noted in 9/15 patients, including in 3 cases associated with repeated use of ACE inhibitors; 2 patients out of 15 had atopy/bronchial asthma in history; family history of AE was absent. All patients received an ACEi/ARB for arterial hypertension; monotherapy was used in 7 out of 15 cases, combination therapy was used in 5 cases out of 15, and 3 out of 15 patients used ACE inhibitors irregularly. The majority (13; 86.7%) of patients had concomitant chronic diseases, and in 53.3%

of cases, they took drugs from other groups together with antihypertensive drugs. In the comparison group, 6 out of 13 patients had AE in the history; 3 out of 13 patients had concomitant atopy or bronchial asthma; in 1 case out of 13, a family history of AE was indicated; concomitant chronic diseases were noted in 11 (84.6%) cases. The level of C-reactive protein was determined in 23 out of 28 patients. An increase in C-reactive protein level was found in 43% of cases in the ACEi/ARB-induced AE group and 22% of cases in the comparison group ($p = 0.39$). The level of the C4 component of complement in the studied medical records was not determined.

Nasopharyngeal and oropharyngeal swabs were taken from all patients for COVID-19 by PCR. A qualitative method performed the determination of IgG/IgM to SARS-CoV-2 by 23 (82%) patients. In the group of patients with ACEi/ARB-induced AE, IgG/IgM was

Table 1. Characteristics of patients with angioedema induced by angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Localization of AE	ICU	ACEi/ARB	Mode of application	Concomitant drugs	AE episodes in the history	IgG/IgM to SARS-COV2	PCR
Tongue, soft palate uvula, lips, cheek	Yes	Captopril + Lisinopril	Single intake	No	Yes /Lisinopril	negative	negative
Lips, cheek	No	Lisinopril	Regular intake for 4 years	No	No	negative	negative
Cheek	No	Enalapril	1 week	Yes	Yes /Lisinopril	-	negative
Lip, cheek	No	Enalapril	Regular intake	Yes	Yes /Enalapril	negative	negative
Face, tongue	No	Enalapril	Regular intake	Yes	Yes	-	positive
Tongue, soft palate, sublingual region	Yes	Enalapril	Regular intake For 6 months	Yes	No	negative.	positive
Face, tongue	No	Losartan	Regular intake	No	Yes	negative	negative
Lips, cheek	No	Enalapril	Regular intake	No	Yes	negative	negative
Face	No	Perindopril	Regular intake	Yes	Yes	IgM positive IgG positive	negative
Tongue	No	Losartan	Regular intake	Yes	No	IgM positive IgG p positive	negative
Soft palate uvula	No	Captopril	Single intake	Yes	Yes	negative	negative
Tongue	Yes	Captopril	Single intake	No	No	negative	negative
Soft palate uvula	No	Captopril + Losartan	Regular intake of Losartan	Yes	No	negative	negative
Lips	No	Lisinopril	Regular intake	Yes	Yes	IgM negative IgG positive	negative
Face	No	Losartan	Regular intake	No	No	-	negative

Note. AE — angioedema; ICU — intensive care unit; ACEi — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; D — drugs; PCR — a polymerase chain reaction.

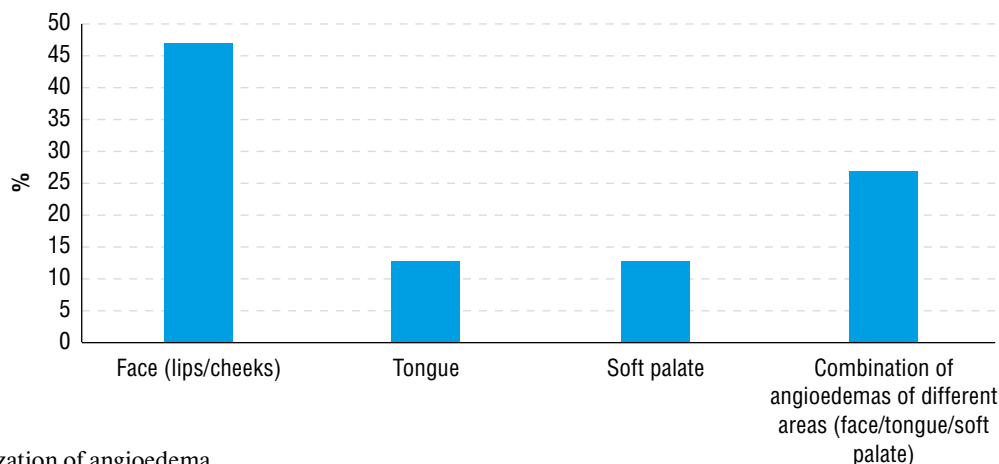


Fig. 1. Localization of angioedema.

determined in 12 cases out of 15. The positive result of IgG to SARS-CoV-2 was detected in 1 case, and those of IgG and IgM were revealed in 2 cases (PCR test result was negative). In 2 cases, a positive PCR test result was obtained, and a concomitant COVID-19 infection was diagnosed. Patients with AE and COVID-19 did not increase body temperature, changes on a chest X-ray, or a decrease in the oxygen level in the blood; there was only an increase in C-reactive protein level and 1 case an increase in the level of D-dimer. AE was localized on the face, tongue, sublingual region, and soft palate.

In the comparison group, the determination of IgG/IgM to SARS-CoV-2 was performed in 11 cases out of 13. Positive IgG results were registered in 2 cases, that of IgM was revealed in 1 case, and those of IgG and IgM were registered in 1 case (PCR test result was negative). In addition, a positive PCR test result was obtained in 1 patient with lip and cheek AE of unclear etiology, and a simultaneous diagnosis of asymptomatic COVID-19 infection was established.

Treatment of AE included parenteral administration of systemic glucocorticoid (dexamethasone), H₁-antihistamines (clemastine, chloropyramine), and, in some

cases, furosemide. In AE patients, while taking ACE inhibitors/ARB, these groups of drugs were cancelled. If basic arterial hypertension therapy was required, they were replaced with antihypertensive drugs from the calcium antagonists and/or thiazide-like diuretics group. All patients had a favorable outcome of AE.

Additional research outcomes

The distribution of patients depending on the type of causative ACE inhibitor/ARB is presented in Fig. 2. The most common causes of AE development were enalapril and captopril. In 2 cases, long-acting ACEi and ARB were used in conjunction with captopril.

Discussion

Summary of the main research outcome

ACEi-induced AE can have life-threatening localization and require hospitalization. An infection caused by SARS-CoV-2 is discussed as a possible trigger for developing this type of AE. In our study, cases of a combination of AE during the intake of an ACE inhibitor and a mild COVID-19 infection were revealed.

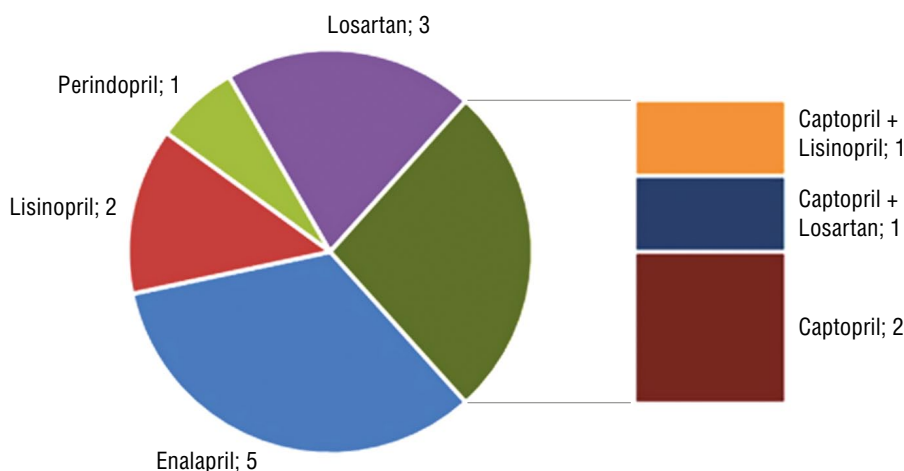


Fig. 2. Causal angiotensin-converting enzyme inhibitors / angiotensin receptor blockers.

Discussion of the main research outcome

AE induced by intake of an ACE inhibitor can obstruct the upper airway and lead to asphyxia. The diagnosis of ACEi-induced AE is established based on clinical and anamnestic data, and there are no diagnostic tests to confirm it. Until now, there is no approved approach of drug therapy for this type of bradykinin AE. Thus, the analysis of clinical characteristics, management approach, and possible trigger factors of AE caused by ACE inhibitors/ARB is important for improving the diagnostics, treatment, and prevention of the development of this potentially life-threatening adverse reaction. Intake of an ACE inhibitor is one of the most common causes of developing isolated AE that requires urgent care [4]. In our study, AE patients taking ACE inhibitors/ARB accounted for about half of all hospitalization cases for isolated AE. According to the literature, risk factors for ACEi-induced AE are over 65 years and female gender [5]. In this study, the median age of patients with AE caused by ACE inhibitors/ARB was 59 years; distribution by gender showed some predominance of men (60%), and such results may be associated with the small size of the study group. Comparable data are presented in the recently published work by A. Pfaue et al. [23]. A retrospective analysis of medical records of patients hospitalized with isolated AE in the otorhinolaryngology department was conducted. The proportion of patients with AE caused by drugs blocking the RAAS (ACE inhibitors, ARB, and renin inhibitors) was 41% (84 out of 203 patients), the average age was 71 years (43–94 years), and the ratio of women to men was 48% and 52%, respectively.

According to our data, enalapril and captopril caused most commonly the development of drug-induced AE, which is associated not with the peculiarities of these molecules but with the frequency of their use. Furthermore, in various studies, the ratio of causative ACE inhibitors/ARB differed depending on the region and the time of their conduct [1, 23, 24].

Localization of AE in the face and oral cavity, established in our study, is typical for this type of AE. With isolated AE of the soft palate uvula, which was noted in 2 cases, differential diagnostics with uvula edema is required due to snoring (taking into account the presence of snoring, sleep disturbances, apnea) [23]. Life-threatening localization of AE, which required hospitalization in the intensive care unit, was established in 20% of patients.

There were no cases of intubation and tracheostomy. A favorable outcome in all cases analyzed was probably due to the timely cancellation of ACE inhibitors/ARB or the independent resolution of AE. The small size of the study group should also be considered. In a study by A. Pfaue et al. [23], the risk of emergency intubation and/or tracheostomy was 9 times higher in patients with AE caused by drugs blocking the RAAS compared with patients with AE induced by other causes (odds ratio 9.077; 95% CI 1.072–76.859). The authors emphasize the importance of doctors who work in emergency de-

partments about the clinical presentation and aspects of therapy for this type of AE [23].

In the study group of patients with ACEi/ARB-induced AE, there was a rather high frequency of repeated episodes (60%), including those associated with repeated intake of ACE inhibitors. Recurrent AE in patients receiving ACEi/ARB may indicate a lack of awareness among doctors about this adverse reaction. The problem of underestimating general practitioners (therapists) of the possibility of bradykinin-mediated AE during therapy with ACE inhibitors is discussed in a recent study by L. Mihaela et al. [24].

The inpatient records we studied also contained indications of the facts of self-medication, which is associated with the possibility of over-the-counter sale of such drugs as captopril, enalapril, and lisinopril. When establishing the diagnosis of AE caused by intake of an ACEi/ARB, it is important to inform the patient about the possibility of a recurrence of edema, despite the cancellation of an ACEi/ARB, and the need to seek emergency help in this case, as well as to explain the danger of self-medication. In addition, it should be borne in mind that ACE inhibitors/ARB can be trigger factors in HAE, acquired AE with deficiency or impairment of the functional activity of the C1 inhibitor, and idiopathic AE. In a study by Z. Balla et al. [25], out of 149 patients with recurrent AE, while taking an ACE inhibitor, 2 patients and 12 other family members were diagnosed with HAE with C1 inhibitor deficiency. In 3 cases, acquired C1 inhibitor deficiency was detected. HAE without C1-inhibitor deficiency is a rare form that, in its clinical presentation, may be similar to ACEi-induced AE, but a family history of AE is typical in it. In this case, genetic testing is required to confirm the diagnosis. In the Republic of Belarus, in the presence of clinical and anamnestic data, the C4 component of complement is determined as a screening for HAE, at the republican level, both immunological (measurement of the levels of C4, C1 inhibitor, C1q, determination of the functional activity of C1 inhibitor) and genetic studies (sequencing the genes *SERPING1*, *FXII*, *ANGPT1*, *PLG*, etc.) are performed [26]. According to the medical records we analyzed, there were no referral cases of patients to republican centers for HAE diagnostics. Patients with relapses of AE need further follow-up and additional examination at the outpatient stage, if necessary.

We were unable to estimate the period from the beginning of intake of an ACE inhibitor to the onset of AE due to insufficient information in the medical documentation. According to the literature, the development of AE is possible both in the early terms (first weeks) and several years after the start of therapy [3]. In a retrospective cohort study by A. Banerji et al. [1], which included 134,945 patients who received an ACE inhibitor, in 0.7% cases, an ACE inhibitor-induced AE developed during the first 5 years of administration. In only 10% of them, AE occurred in month 1 of therapy. The possibility of AE development during the long-

term therapy with ACE inhibitors/ARB complicates the diagnostics, and the factors contributing to the development of AE often remain unclear. Studies have been published in which an increase in C-reactive protein level was noted in AE induced by ACE inhibitors/ARB. In addition, the role of inflammatory stimuli in the emergence or maintenance of AE in some patients was suggested [23, 27].

In December 2019, an epidemic of a new infectious disease called COVID-19 began in China, caused by a representative of the coronavirus family, SARS-CoV-2, which spread worldwide. Endothelial dysfunction and increased vascular permeability are characteristic pathological signs of COVID-19 [28]. These phenomena can lead to increased fluid extravasation and increased risk of AE. The protective effects of ACE inhibitors/ARB are believed to be associated with an increase in the expression of ACE2 and inhibition of excessive RAAS activity through a decrease in the effects of AT-II. The binding of SARS-CoV-2 to the ACE2 receptor can lead to suppression of surface regulation of ACE2, thereby reducing its protective effects and aggravating the adverse effects of AT-II. A decrease in ACE2 expression disrupts its role in the cleavage of several substrates, including BK metabolites [18, 28].

In the described cases of the development of AE during the intake of ACE inhibitors and COVID-19 infection, the new coronavirus infection is considered a possible trigger factor. Infection with SARS-CoV-2 can be a “second blow” that leads to edema in patients receiving this group of drugs. Management approach consisted in cessation of an ACE inhibitor; in addition, in 2 cases, systemic glucocorticoids and antihistamines were used [20, 21], and in 1 case, tranexamic acid was used [18]. A case of urticaria with AE as a premonitory symptom of COVID-19 infection has also been published. The role of histamine and BK in the development of AE, in this case, is discussed [29]. The course of COVID-19 infection is highly variable. In the analyzed cases of the combination of ACEi-induced AE and COVID-19, the symptoms of AE prevailed in the clinical presentation. The signs of an upper respiratory tract infection (rhinitis, sore throat) were probably concealed by symptoms of edema of the oropharyngeal mucous membrane. In the comparison group, a case of a combination of isolated AE of the lips and a face with an asymptomatic course of COVID-19 was established.

Study limitations

The limitations of this study were its retrospective nature and the short duration of the period analyzed.

Conclusion

Due to their proven efficacy in treating many cardiovascular diseases, ACE inhibitors and ARB are widely used in clinical practice. However, until now, AE caused by intake of ACEi/ARB remains a complication

of pharmacotherapy, which is difficult to diagnose, with insufficiently studied mechanisms of formation and approaches to treatment. Patients with ACEi-induced AE may require hospitalization to monitor the patency of the upper airway. The most common causes of drug-induced AE among the analyzed cases were enalapril and captopril. In patients with AE, while taking ACE inhibitors, cases of mild COVID-19 infection were revealed with a predominance of AE symptoms in the clinical presentation with localization in the face, tongue, sublingual region, and soft palate.

With the development of AE, a targeted collection of anamnesis is required regarding the use of ACEi/ARB and the symptoms of COVID-19, as well as PCR examination for COVID-19 infection.

Questions requiring further research include the effect of infection with SARS-CoV-2 on the levels of BK and its metabolites; the triggering role of COVID-19 infection in the development of AE in patients receiving ACEi/ARB; recommendations for the management of patients with ACEi-induced AE and a positive result for COVID-19.

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