# Angioedem uzrokovan lijekovima koji djeluju na angiotenzinski sustav

**Batinac, Tanja; Plazonić, Željko; Bukvić, Marija**




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# Angioedema Caused by Agents Acting on the Angiotensin System

**Tanja Batinac***, **Željko Plazonić**, **Marija Bukvić**

Klinički bolnički centar Rijeka, Rijeka, Hrvatska
University Hospital Centre Rijeka, Rijeka, Croatia

**SAŽETAK:** Blokatori reninsko-angiotenzinskog sustava (RAS) često su primjenjivani lijekovi s dokazanim pozitivnim utjecajem na kardiovaskularne i bubrežne bolesti. Lijekovi koji utječu na RAS dijele se u četiri skupine, od kojih su najčešći inhibitori angiotenzinkonvertirajućeg enzima (ACEI) te blokatori angiotenzinskih receptora (ARB). Ti se lijekovi općenito smatraju sigurnima i djelotvornima u većine pacijenata, no u nekim slučajevima može doći do nuspojava. Angioedem uzrokovan blokatorima RAS-a rijedak je, no potencijalno smrtonosan događaj. Kako je zadnjih nekoliko godina došlo do eksponencijalnog porasta uporabe blokatora RAS-a u cijelome svijetu, prisutna je povećana prevalencija angioedema uzrokovanog ovom skupinom lijekova.

**SUMMARY:** Rennin angiotensin system (RAS) blockers are commonly used drugs with proven benefits for cardiovascular and renal diseases. There are four classes of drugs acting on the angiotensin system, the most commonly used being angiotensin converting enzyme inhibitors (ACEI) followed by angiotensin receptor blockers (ARB). These drugs are generally considered safe and effective in the majority of patients, but in some cases adverse drug reactions may occur (ADRs). Angioedema resulting from RAS blocker treatment is a rare but potentially life-threatening event, and we should keep in mind that in recent years the exponential growth of the use if RAS blockers has been evident worldwide, resulting in increased prevalence of angioedema induced by RAS blockers in these patients.

**KLJUČNE RIJEČI:** nuspojave lijekova, angioedem, inhibitori angiotenzinkonvertirajućeg enzima, blokatori reninsko-angiotenzinskog sustava.

**KEYWORDS:** adverse drug reaction, angioedema, angiotensin converting enzyme inhibitors, renin angiotensin system blockers.

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***ADDRESS FOR CORRESPONDENCE:** Tanja Batinac, Klinika za dermatovenerologiju, Klinički bolnički centar Rijeka, Krešimirova 42, HR-51000 Rijeka, Croatia. / Phone: +385-51-658-281 / E-mail: tanjabatinac@net.hr

**ORCID:** Tanja Batinac, http://orcid.org/0000-0002-3482-1937 / Željko Plazonić, http://orcid.org/0000-0002-3769-9754 Marija Bukvić, http://orcid.org/0000-0003-0625-8056

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## Uvod

Blokatori reninsko-angiotenzinskog sustava (RAS) često su primjenjivani lijekovi s dokazanim pozitivnim utjecajem na kardiovaskularne i nefrološke bolesti kao što su zatajivanje srca, arterijska hipertenzija, stanje nakon infarkta miokarda te bubrežne bolesti[1]. Danas postoje četiri skupine lijekova koje djeluju na angiotenzinski sustav: inhibitori angiotenzinkonvertirajućeg enzima (ACEI), blokatori angiotenzinskih receptora (ARB), agonisti aldosterona (AA) te direktni inhibitori renina (DRI), no najprimjenjivaniji su ACEI. Ti se lijekovi općenito smatraju sigurnima i djelotvornima u većine pacijenata, no u nekim slučajevima mogu

## Introduction

Renin angiotensin system (RAS) blockers are commonly used drugs with proven effectiveness for cardiovascular and renal diseases such as heart failure, hypertension, post myocardial infarction, and kidney diseases[1]. Today, there are four classes of drugs acting on the angiotensin system including: angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone agonists (AA), and direct renin inhibitors (DRI), but the most commonly used are ACEI. These drugs are generally considered safe and effective in the majority of patients, but in some cases adverse drug reac-

nastupiti nuspojave. Najčešća je nuspojava suhi kašalj, koji se pojavljuje u oko 9 % pacijenata liječenih ACEI-om te u oko 2 % liječenih ARB-om[2]. U rijetkim se slučajevima u pacijenata razvija za život opasan angioedem koji najčešće zahvaća područja glave i vrata te se pojavljuje u 0,1 – 2,5 % liječenih pacijenata, prema podatcima iz različitih studija[3-5].

## Klinička slika i dijagnoza

Angioedem ili Quinckeov edem nagla je, prolazna, lokazirana oteklina dubokoga retikularnog dermisa ili potkožnog ili submukoznog tkiva[6]. Uzrokuju ga vazodilatacija i povećana permeabilnost endotela, što dovodi do ekstravazacije tekućine u međustanični prostor[6,7]. Angioedem uzrokovan blokatorima RAS-a nije alergijske prirode te češće zahvaća područja glave i vrata, a tek rijetko organe. Razvija se u području rahloga vezivnoga tkiva za 4 – 6 sati, a nestaje unutar 24 – 48 sati. Oteklina može biti asimetrična te najčešće zahvaća lice, usnice, jezik i gornje dišne putove[6,8]. U nekim slučajevima dolazi do klinički značajne opstrukcije gornjih dišnih putova koja može biti opasna za život ili čak smrtonosna[6,8]. U pacijenata se razvijaju simptomi kao što su „knedla" u grlu, promukli glas i teškoće pri disanju i gutanju, koji upućuju na opstrukciju dišnih putova[6,9]. Angioedem uzrokovan blokatorima RAS-a pokatkad se pojavljuje kao osip ili edem koji zahvaća gastrointestinalno ili genitalno područje ili neko drugo područje izvan glave i vrata[8,10,11]. Nema izravnog testa za dijagnozu angioedema uzrokovana lijekovima koji djeluju na RAS, a nema ni načina da se predvidi rizik da će se u bolesnika razviti angioedem nakon početka liječenja. U akutnoj je fazi dijagnoza postavljena na temelju kliničke slike i anamnezom te se sastoji od isključivanja drugih uzorka angioedema. Ostale vrste angioedema uključuju: nasljedni ili stečeni (uzrokovan bradikininom ili vazoaktivnim molekulama), alergijski ili pseudoalergijski (ovisan o degranulaciji mast-stanica) te idiopatski angioedem[6,8,9,12,13].

Angioedem najčešće nastaje unutar 1 – 3 mjeseca od početka liječenja, no simptomi se mogu pojaviti više mjeseci, godina ili čak desetljeća nakon početka liječenja[3,4,14,15]. To izrazito otežava dijagnozu angioedema uzrokovana blokatorima RAS-a. Nakon povlačenja lijeka sklonost razvijanju angioedema se smanjuje, no može ostati prisutna mjesecima ili čak godinama[16,17]. To nije u skladu sa standardnim kriterijima procjene akutnih nuspojava. Predložena je hipoteza da do ponovnog nastanka angioedema nakon ukidanja lijeka dolazi zbog podraženosti intrinzične, već postojeće osjetljivosti na angioedem, koja je još nejasne etiologije.

Nastanak angioedema tijekom liječenja ACEI-om češći je nego pri liječenju drugim blokatorima RAS-a[4,8]. No pacijenti u kojih se razvio angioedem tijekom liječenja ACEI-om također mogu ponovno razviti angioedem nakon prebacivanja na liječenje ARB-om, i to u oko 4 % slučajeva. Najnovije metaanalize upućuju na to da prethodna epizoda angioedema na ACEI stvara predispoziciju za nastanak angioedema na ARB u takvih pacijenata[18,19].

## Čimbenici rizika

Otkriveno je nekoliko čimbenika rizika vezanih za nastanak angioedema tijekom primjene ACEI-a[6,20], no poznavanje čimbenika rizika vezanih za angioedem uzrokovan ARB-om

tions may occur (ADRs). The most common ADR is persistent dry cough that occurs in about 9% of patients treated with ACEI and in about 2% treated with ARB[2]. Rarely, patients develop potentially life-threatening angioedema usually affecting the head and neck regions and occurring in 0.1-2.5% of treated patients according to data reported from different studies[3-5].

## Clinical presentation and diagnosis

Angioedema or Quincke's edema is an abrupt, transient, localized swelling of the deep reticular dermis or subcutaneous or submucosal tissues[6]. It is caused by vasodilatation and increased endothelial permeability, resulting in extravasation of fluid into the interstitial compartment[6,7]. Angioedema caused by RAS blockers is non-allergic in nature and more frequently affects the head and neck regions and the viscera only occasionally. It develops in the area of loose connective tissue over 4-6 h and usually resolves within 24-48 h. The swelling may be asymmetrical and most often affects the face, lips, tongue, and upper airways[6,8]. In some cases, clinically significant obstruction of the upper airway can be life-threatening and sometimes even fatal[6,8]. Patients develop symptoms such as a lump in the throat, hoarse voice, and difficulties breathing or swallowing as a signs of impending airway obstruction[6,9]. Angioedema induced by ARS blockers occasionally presents with urticaria or edema affecting gastrointestinal, genital, or regions other than the head and neck region[8,10,11]. There is no specific test for the diagnosis of angioedema triggered by drugs acting on the angiotensin system, and no means to predict the risk that a patient will develop angioedema after initiating treatment. The diagnosis in the acute phase is clinical and anamnestic, including exclusion of other causes of angioedema. Other types of angioedema include: hereditary or acquired (mediated by bradykinin or vasoactive molecules), allergic or pseudoallergic (dependent on mast cell degranulation), and idiopathic angioedema[6,8,9,12,13].

Angioedema generally occurs within the first 1-3 months of therapy, but symptoms may appear months, years, or even decades after treatment initiation[3,4,14,15]. This makes diagnosis of RAS blockers-induced angioedema quite difficult. After drug withdrawal, the tendency to develop angioedema usually decreases but may persist for months and even years[16,17]. This is not in accordance with the standard criteria for assessment for acutely occurring ADRs. It has been suggested that reoccurrence of angioedema after discontinuation of the incriminated drug reflects exacerbation of an intrinsic underlying susceptibility to angioedema of unclear etiology.

Angioedema developing during ACEI treatment is more frequent than in other RAS blockers[4,8]. However, patients who have experienced ACEI angioedema can also develop angioedema when switched to ARB treatment, in about 4% of patients. Recent meta-analyses suggested that a previous episode of ACEI angioedema predisposes patients to develop ARB-induced angioedema[18,19].

## Risk factors

Several risk factors have been identified in triggering angioedema during ACEI treatment[6,20], but the knowledge about risk factors contributing to angioedema induced by ARBs or

ili drugim blokatorima RAS-a oskudno je, prije svega zbog njegove rijetkosti[21]. Glavni čimbenici rizika uključuju rasu (afrički predci), dob nakon 65. godine života, pušenje[22], ženski spol, anamnestičke podatke o nasljednom, stečenom ili idiopatskom angioedemu, uporaba pojedinih lijekova (acetilsalicilatna kiselina, nesteroidni antiinflamatorni lijekovi, beta-laktamski antibiotici, inhibitori dipeptidil peptidaze IV, imunosupresivi), traumu respiratornoga tkiva, anamnestičke podatke o osipu izazvanom lijekovima te sezonskim alergijama, koronarnu bolest srca te kronično zatajivanje srca[3,4,9,22,23].

## Patofiziološki mehanizmi

Iako nisu razjašnjeni točni patofiziološki mehanizmi odgovorni za nastajanje angioedema tijelom liječenja blokatorima RAS-a smatra se da je posredovan razinom bradikinina ili drugih vazodilacijskih molekula[6,9,12]. Isprva se smatralo da su odgovorni samo ACEI zbog izravnog pojačanja bradikininske aktivnosti, no ubrzo nakon uvođenja ARB-a i DRI-a u kliničku praksu postalo je očito da i ti lijekovi mogu potaknuti angioedem[24,25]. Angiotenzinkonvertirajući enzim (ACE) ima dva aktivna mjesta koja mogu razgraditi bradikinin u neaktivne metabolite i prevesti angotenzin I u angiotenzin II. Postoje alternativni putovi inaktivacije bradikinina koji mogu biti oslabljeni zbog genskih varijacija, dovodeći do nakupljanja bradikinina[9]. Budući da se samo u manjine pacijenata razvije angioedem, smatra se da spomenuti lijekovi možda samo potiču angioedem u genetski predisponiranih pojedinaca. Nekoliko je genskih polimorfizama nedavno povezano s povećanim rizikom od angioedema zbog nedostatka nekolicine enzima koji sudjeluju u degradaciji bradikinina, pogotovo kad je ACE inhibiran. Otkrivene su varijante u genima koji određuju aminopeptidazu P i metalo-endopeptidazu, koji su uključeni u degradaciju bradikinina u inaktivne metabolite[26-28].

Za razliku od ACEI-a, ARB nemaju nikakav izravan utjecaj na ACE ili degradaciju bradikinina. Smatra se da ARB povećavaju razinu bradikinina neizravnom inhibicijom ACE i metalo-endopeptidaze[29] zbog povišene razine cirkulirajućeg angiotenzina II koji je na raspolaganju za vezanje na angiotenzinski receptor tipa 2, a rezultat je blokiranje receptora tipa 1[30].

## Liječenje

Liječenje angioedema u pacijenata koji primaju blokatore RAS-a počinje zaustavljanjem lijeka na koji se sumnja da je uzrokovao angioedem. Pacijentu se preporučuje da nikada više ne uzima nijedan lijek iz te skupine. Križna reaktivnost ozbiljan je problem pri pripisivanju blokatora RAS-a. Pacijent koji razvije angioedem tijekom liječenja ACEI-a ima rizik od prosječno 10 % da će se u njega ponovno razviti angioedem pri liječenju angiotenzin II agonistima, primjerice sartanima[31,32]. Stoga se za slabo tolerantne pacijente prebacivanje s jednog blokatora RAS-a na drugi predlaže samo kad su očekivane pozitivne posljedice mnogo veće od rizika, a nakon prebacivanja na drugi lijek treba uvesti pomno praćenje pacijentova stanja. DRI, kao i aliskiren, pojavili su se kao alternativa za takve pacijente, no i kod njih je nedavno otkrivena povezanost s angioedemima[25].

Antihistaminici, kortikosteroidi i epinefrin, često primjenjivani lijekovi pri liječenju angioedema, nemaju nikakav učinak

other RAS blockers is poor, generally due to its rarity[21]. Major risk factors include race (African ancestors), age over 65 years, smoking[22], female sex, history of hereditary, acquired, or idiopathic angioedema, use of certain drugs (aspirin, non-steroidal anti-inflammatory drugs, beta-lactam antibiotics, dipeptidyl peptidase IV inhibitors, immunosuppressants), respiratory tissue trauma, history of drug rash and seasonal allergies, coronary artery disease, and chronic heart failure[3,4,9,22,23].

## Pathophysiological mechanism

Although the precise pathophysiological mechanism responsible for angioedema developing during RAS blockers treatment has not been elucidated, it is believed to be mediated by bradykinin levels and other vasodilating molecules[6,9,12]. Initially, only ACEI were considered responsible due to their ability to directly increase bradykinin activity, but soon after introducing ARB and DRI into clinical practice it became evident that these drugs could also trigger angioedema[24,25]. Angiotensin converting enzyme (ACE) has two active sites able to degrade bradykinin to inactive metabolites and convert angiotensin I to angiotensin II. Inhibition of ACE by ACEI decreases the degradation of bradykinin and formation of angiotensin II. There are alternative bradykinin inactivation pathways that can be deficient due to genetic variants, leading to accumulation of bradykinin[9]. Since only a minority of patients develops angioedema, it is believed that these drugs may facilitate angioedema in genetically predisposed individuals. Recently, several genetic polymorphisms have been associated with increased risk of angioedema due to the deficiency of several enzymes involved in the degradation of bradykinin, especially when ACE is inhibited. Variants have been detected in the gene encoding aminopeptidase P and the metallo-endopeptidase gene involved in bradykinin degradation to inactive metabolites[26-28].

Contrary to ACEI, ARBs have no direct influence on ACE or bradykinin degradation. It is believed that ARBs increase bradykinin levels through indirect inhibition of ACE and metallo-endopeptidase[29], due to increased levels of circulating angiotensin II available for binding to the angiotensin type 2 receptor, as a result the type 1 receptor being blocked[30].

## Treatment

The therapeutic management of angioedema in patients treated by RAS blockers starts by stopping the suspected drug once the diagnosis is suspected. The patient is advised not to take any drug of the same class again. Cross-reactivity is an important concern when prescribing RAS blockers. A patient who developed angioedema during ACEI treatment has an average 10% risk of developing it again if taking an angiotensin II agonist, such as sartans[31,32]. Thus, it has been suggested that switching an intolerant patient from one RAS blocker to the other should be considered only when the benefit strongly outweighs the risk. In addition, close monitoring must be implemented after switching. DRI, like aliskiren, appeared as an alternative for these patients, but recently it has also been associated with angioedema[25].

Antihistamines, corticosteroids, and epinephrine, commonly used drugs in treatment of angioedema, have little or no effect on bradykinin-induced angioedema. Considering the patho-

na angioedem uzrokovan bradikininom. Uzimajući u obzir patofiziološki fenomen angioedema potaknutog blokatorima RAS-a, molekula koja se čini najboljim izborom za liječenje jest icatibant (Fyrazyl®, Shire Orphan Therapies Inc., St. Helier, Jersey, SAD). To je blokator B2-receptora čija je učinkovitost unutar prvog sata od primjene već dokazana[33]. Učinkovitost u koncentriranju inhibitora C1 esteraze (Berinert®) čini to najboljim izborom za liječenje nasljednog ili stečenog angioedema, kao što je pokazano u prikazima slučajeva angioedema potaknutih blokatorima RAS-a[34]. Učinkovitost Ecallantide®, inhibitora plazmatskog kalikreina, još nije istražena. Svježe smrznuta plazma sadržava prirodne angiotenzinkonvertirajuće enzime i inhibitore C1 esteraze. Uzima se u obzir za liječenje kad druge terapijske mogućnosti nisu na raspolaganju, jer je pokazano da uspješno i brzo liječi angioedem uzrokovan ACEI-om[35].

## Zaključak

Sve dok nam više podataka ne bude na raspolaganju, zbog sve veće popularnosti blokatora RAS-a potrebno je povećati svijest i educirati liječnike o mogućim nuspojavama. Iako je angioedem uzrokovan liječenjem blokatorima RAS-a rijetka pojava, treba držati na umu da je zadnjih nekoliko godina eksponencijalni rast uporabe blokatora RAS-a primijećen diljem svijeta, što je dovelo do povećane zastupljenosti angioedema te povećanja broja dana bolničkog liječenja, trošenja zdravstvenih resursa i potencijalnog gubitka života[36].

physiological phenomenon of angioedema triggered by RAS blockers, the molecule that seems to be the treatment of choice is icatibant (Fyrazyl®, Shire Orphan Therapies Inc., St. Helier, Jersey, USA). This is a blocker of B2 receptors, shown to be effective in the first hour after administration[33]. The effectiveness of C1 esterase inhibitor concentrate (Berinert®) makes it the treatment of choice in hereditary or acquired angioedema, as has been demonstrated in case reports of angioedema triggered by RAS blockers[34]. The effectiveness of Ecallantide®, an inhibitor of plasma kallikrein, has not yet been studied. Fresh frozen plasma contains natural angiotensin converting enzymes (ACE) and C1 esterase inhibitors. It is considered for treatment when other therapeutic options are unavailable, since it has been shown to effectively and rapidly treat angioedema due to ACEI[35].

## Conclusion

Until more data is available, due to the increased popularity of RAS blockers attempts should be made to improve awareness and educate clinicians about possible ADR caused by these drugs. Even though angioedema resulting from RAS blocker treatment is a rare event, we should keep in mind that in recent years the exponential growth of the usage of RAS blockers has been evident worldwide resulting in increased prevalence of angioedema induced by RAS blockers along with an increase in hospitalization, health care resource consumption, and potential loss of lives[36].

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