OPIS PRZYPADKU / CASE REPORT
Otrzymano/Submitted: 11.11.2020 • Zaakceptowano/Accepted: 17.12.2020

Candesartan-induced angioedema – case report
Obrzęk naczynioruchowy po kandesartanie – opis przypadku

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Summary

Background. Sartans, or antagonists of the AT1 receptor for angiotensin II (ARB, angiotensin II type 1 receptor blockers), are drugs that block the receptor action of angiotensin II. They are used in the treatment of hypertension and heart failure. In antihypertensive therapy, they are recommended for patients with organ damage, coexisting kidney diseases and after a stroke. Sartans may cause few adverse reactions, such as secondary hypotension, renal dysfunction and hyperkalemia, however it is a group of drugs with the lowest rate of adverse effects. One of the rarely occurring ADRs reported with the use of sartans is angioedema. ***Material and methods.*** We describe a case report of a 38-year-old woman who experienced an adverse reaction of angioedema during the therapy with candesartan. ***Results***. Symptoms resolved after discontinuation of candesartan and administration of medications recommended for the treatment of angioedema. The patient was advised to discontinue the candesartan therapy and was prescribed amlodipine at a dose of 5 mg/day as an antihypertensive drug. ***Conclusions.*** The described case confirms the risk of adverse reactions as a consequence of candesartan therapy. *(Farm Współ 2020; 13: 218-222)*

Key words: *candesartan, angioedema, Quincke's edema*

Streszczenie

Wstęp. Sartany, czyli antagoniści receptora AT1 dla angiotensyny II (ARB, angiotensin II type 1 receptor blocker), to leki blokujące receptorowe działanie angiotensyny II. Stosowane są w terapii nadciśnienia tętniczego i niewydolności serca. W terapii hipotensyjnej są preferowane u chorych z uszkodzeniami narządowymi, ze współistniejącą chorobą nerek i po przebytym udarze mózgu. Sartany mogą powodować działania niepożądane, takie niedociśnienie tętnicze wtórne, zaburzenia pracy nerek czy hiperkaliemię, jednak jest to grupa leków najrzadziej wywołująca działania niepożądane. Jednym z bardzo rzadkich działań niepożądanych obserwowanym podczas stosowania sartanów jest obrzęk naczynioruchowy. ***Materiał i metody.*** Przedstawiamy przypadek 38-letniej kobiety leczonej kandesartanem, u której wystąpił obrzęk naczynioruchowy. ***Wyniki.*** Objawy ustąpiły po odstawieniu kandesartanu i zastosowaniu leków zalecanych w terapii obrzęku naczynioruchowego. Pacjentce zalecono zaprzestanie dalszego stosowania kandesartanu, natomiast jako lek hipotensyjny zalecono amlodypinę w dawce 5 mg/dobę. ***Wnioski.*** Opisany przypadek potwierdza ryzyko wystąpienia działań niepożądanych jako następstw terapii kandesartanem. *(Farm Współ 2020; 13: 218-222)*

Słowa kluczowe: *kandesartan, obrzęk naczynioruchowy, obrzęk Quinckego*

Introduction

Angiotensin II receptor type 1 (AT1) antagonists (angiotensin II receptor blockers- ARB), also called sartans, constitute a group of drugs with a common mechanism of action involving inhibition of angiotensin II receptor type 1 (AT1), which prevents the action of angiotensin II released by the renin-angiotensin-aldosterone system (RAAS) [1]. ARB have relevant applications to ACEI (Angiotensin-converting enzyme inhibitors) and are applicable in the treatment of diseases such as hypertension, congestive heart failure and chronic kidney diseases. In contrast to ACEI, ARBs have no impact on bradykinin levels, a peptide hormone, which causes bronchial smooth muscle contraction manifested by coughing and can

lead to angioedema. The ACE-I-induced angioedema incidence is estimated to be 0.1 to 0.7%; however, about one-third of all emergency department visits for angioedema was resulted from ACEI. Angioedema, also known as Quincke edema, is a rare complication of sartan therapy [2].

Case report

A 38-year-old patient reported to the family doctor (an online consultation) with a week-long headache and dizziness. The analgesic therapy used at that time (acetaminophen 3 g/day or metamizole 3 g/day or ketoprofen 100 mg/day) did not relieve the symptoms. Home blood pressure measurements for the next 5 days showed elevated values – 165/100 mmHg. So far, the patient had taken occasional blood pressure measurements, which always showed normal values. Candesartan at a dose of 16 mg/day was recommended as an antihypertensive drug. On the second day of the therapy, the patient noticed swelling affecting the mouth, cheeks, eyelids and hands. The patients treated the symptoms at home using oral preparations of calcium 600 mg and quercetin 120 mg and topical preparation of 1% hydrocortisone. Lack of improvement and swelling of the tongue causing problems with speech, swallowing and closing the mouth prompted the patient to visit the emergency department, where she was given hydrocortisone 200 mg and clemastinum 2 mg (i.m.). The patient did not report any allergic reactions to other drugs and foods. Candesartan-associated angioedema was diagnosed. After the incident of angioedema, antihypertensive drug was changed to amlodipine. Her medical history did not confirm any diseases requiring pharmacotherapy. The patient has been using a dietary supplement containing vitamin D3 (2000 IU/day) and combined preparation (25 mg rutosidum trihydricum and 100 mg acidum ascorbicum) for a few months.

Discussion

Candesartan is used for the management of hypertension and heart failure, as it effectively lowers both systolic and diastolic blood pressure in patients with essential hypertension, regardless of age and gender [3]. It can be applied both as a monotherapy and in a combination formulation containing low-dose thiazide diuretic, hydrochlorothiazide, to support its antihypertensive effect [4]. Candesartan is administered orally (available as 4 mg, 8 mg, 16 mg, and 32 mg tablets and oral suspensions for patients with swallowing difficulties) as candesartan cilexetil [4]. This ARB is rapidly and wholly hydrolyzed by carboxylesterase during its absorption in the intestinal tract to the active metabolite candesartan. Candesartan is a specific and selective antagonist of the AT1 receptor for angiotensin II, which has more than 10,000 times greater affinity for the AT1 receptor than for AT2 (even high concentrations of angiotensin II (Ang II) does not displace it from the receptor), and thus does not block the beneficial cardiovascular effects of stimulation of the latter. The strong binding of candesartan to AT1 receptor diminishes the problem with patients who skip their dose and provides effective blockade even at high concentrations of Ang II [5]. Blocking the AT1 receptor leads to a reduction in arterial and, at a later stage, venous vasoconstriction, which in turn reduces blood pressure. Part of the vasodilation effect results from the reduction of the number of free radicals neutralizing nitric oxide, that would arise during AT1 receptor stimulation. The second mechanism of the drug's antihypertensive action is the intensification of diuresis and natriuresis, largely associated with a decrease in aldosterone levels. The third mechanism is the effect of sartan on the sympathetic nervous system, relying on the blockade of presynaptic AT1 receptors responsible for the norepinephrine release. Additionally, the stimulation of AT1 receptors leads to hypertrophy of the vascular muscle and the left ventricle. Blocking the AT1 receptors reduces the intensity of this process, thus limiting the increase in peripheral vascular resistance and left ventricular hypertrophy. Reducing hypertrophy of the vascular muscles and left ventricular hypertrophy results in lower blood pressure values, as well as a lower overall cardiovascular risk of the patient [3,5]. Candesartan's bioavailability ranges between 15 to 40% due to incomplete absorption [5,6] Candesartan volume of distribution is quite low (0.13 L/kg) as this metabolite is highly bound to plasma proteins. The hypotensive effect after a single administration of a single dose of candesartan appears after about 2 hours. The effective half-life of candesartan cilexetil is longer than the plasma half-life of 4-9 h, reflecting its tight and prolonged binding to the AT1 receptors. With long-term use of candesartan, most of the antihypertensive effect is evident after 2 weeks, and the full effect after 4-6 weeks of regular pharmacotherapy [3,5]. The drug is inactivated to a small extent by hepatic metabolism (CYP 2C9) and primarily eliminated unchanged via the urinary and biliary tracts [6]. Candesartan has minimal drug-drug interactions [7].

Adverse drug reactions (ADRs) and safety of candesartan

Angioedema, also known as Quincke's edema, is described as a vascular reaction of deep dermal, subcutaneous, mucosal, or submucosal tissues characterized by localized increased permeability of blood vessels resulting in tissue swelling. It may involve the area of the whole body, but with the tendency to appear in the area of the face (lips, eyelids, tongue, neck, and upper airways) and genitalia as the structure of the skin is more lax than in other parts of the body. Apart from that, organs of the upper respiratory tract may also be affected, which may result in the occurrence of life-threatening laryngeal edema. This condition usually lasts for 1 to 3 days depending on the causative factors and their treatment. Besides drugs, other factors leading to angioedema can be certain foods, genetic disorders, infections, allergies. The majority of the causes are dependent upon the release of either bradykinin and/or mast cell mediators, such as histamine [8-11]. Drug-induced angioedema can be induced by a broad range of medications, including non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, radiocontrast media, proton pump inhibitors, statins, fibrinolytic agents, estrogens, diuretics, calcium channel antagonists, β-adrenolytics, psychotropic drugs mainly selective serotonin reuptake inhibitors, ACEI and angiotensin II receptor antagonists [10]. Analogous to ACEI-induced angioedema, ARB-induced angioedema may appear with a considerable variation in lag time from 24 h to several months [12,13]. However, instances of angioedema associated with ARBs have been reported, but the mechanism remains indistinct. It was demonstrated, that ARB treatment may increase the serum bradykinin level in hypertensive patients by a similar pathway to ACE inhibitors [9]. There are few theories explaining ARB-induced angioedema. One of them suspects that stimulation of the angiotensin II receptor activates the bradykinin-prostaglandin-nitric oxide cascade, leading to bradykinin-mediated reactions from both ARBs and ACE inhibitors [14]. According to another theory, ARBs may affect the kinin system through the same mechanisms as ACE inhibitors, which may act as antigens binding to IgE on mast cells and basophils, and then leading to induction of cell degranulation, causing the release of bradykinin and other vasoactive agents [12]. An example of ARB-induced angioedema is a case of a 53-year-old woman, with medical history of hypertension, anxiety, depression, and hiatal hernia. She was treated with candesartan 16 mg/day (for over a year after a trial with an ACE inhibitor resulted in an intolerable cough), hydrochlorothiazide 25 mg/day, omeprazole 20 mg/day, and vitamins (OTC). The patient came to the emergency room one morning after waking with very large, swollen tongue, complaining of difficulty speaking, swallowing, and closing her mouth (she had never experienced such ailments before). The patient did not experience symptoms such as wheezing, shortness of breath, nasal breathing difficulties, neck swelling, edema, or skin color abnormalities. She confirmed being allergic to metronidazole, tetracycline, and alcohol but not to any foods. She was treated with intravenous epinephrine, diphenhydramine, famotidine, and methylprednisolone. The patient was diagnosed with candesartan-associated angioedema and admitted to the intensive care unit where she was given diphenhydramine 25 mg every 4 hours, famotidine 20 mg twice/day, methylprednisolone 125 mg every 6 hours, and 5% dextrose in normal saline at 75 ml/hour. The swelling of the tongue resolved by the next morning. The patient was instructed to discontinue candesartan and avoid ACE inhibitors and ARBs [15]. Wesołowska et al. presented a case of a 74-year-old man, initially treated in the otorhinolaryngology ward due to acute dyspnoea in the course of laryngeal edema. The patient experienced sudden swelling of the subcutaneous and submucosal tissues, including the larynx and throat. He was diagnosed with Quincke's angioedema, which could be related to the intake of candesartan. The patient's history had long-term arterial hypertension and intolerance to ACE inhibitors and analgesics. He suffered from iatrogenic hypothyroidism and hypocalcemia. The cause of angioedema in the described patient could be both the use of candesartan in antihypertensive therapy and the state of hypocalcaemia [16]. Kim et al. conducted a review to analyze the medical records of adults, who had been prescribed ARB (candesartan, valsartan, fimasartan, irbesartan, olmesartan, telmisartan and eprosartan) and diagnosed with angioedema between 2009 and 2015. The total number of participants was 35 584- 24 patients diagnosed with angioedema for other reasons prior to their first prescription of ARB were excluded from the study. Angioedema related to ARBs was suspected in 6 of 35 560 patients (0.02%) and its manifestation ranged from several days to several years. Some patients continued the therapy

with ARBs, additionally receiving intermittent antihistamine or steroid medications- in these cases symptoms did not completely resolve, but they did improve. However, the symptoms may be recurrent and the diagnosis can be delayed. These cases makes it more difficult to definitively diagnose ARB-related angioedema. The exact mechanism of the occurrence of the ARB-induced angioedema still remains not entirely explained. Thus, in order to fully understand the pathogenesis of angioedema in case of ARB treatment, more research is required [9,13]. Among the most frequently occurring adverse reactions reported for candesartan are symptomatic hypotension (18.8% – most common in patients who are volume – or salt-depleted due to dietary restriction, dialysis, diarrhea, emesis, or diuretic use), abnormal renal function (12.5%), and hyperkalemia (6.3%). Headache, back pain, angioedema, and upper respiratory tract infections were also reported, but these are rather rare reactions [4]. Risk of side effects, especially hypotension, hyperkalemia and worsening of renal function (including acute renal failure) may increase when candesartan is used concomitantly with an ACE inhibitor [17]. Candesartan has also been linked to the instances of acute liver injury. It can be manifested with either hepatocellular or cholestatic serum enzyme pattern with acute hepatitis- or cholestatic hepatitis-like clinical syndrome [7,18]. The literature also mentions about photosensitivity reactions to sartans, which is a problem of not exactly known prevalence and is probably underdiagnosed [19]. The overdose of candesartan may result in symptomatic hypotension, dizziness, and reflexive tachycardia [4]. A piece of crucial information is that candesartan has a black box warning for fetal toxicity. Drugs interfering with the renin-angiotensin-aldosterone system diminish fetal renal function when used in the second or third trimesters of pregnancy. Impaired renal function increases the risk of morbidity and death-neonates may develop renal failure, hypotension, skull hypoplasia, lung hypoplasia, and can ultimately lead to death [4].

Conclusion

Angioedema is a condition that threatens the health and life of the patient. Sartans are a relatively new group of drugs less commonly associated with this adverse reaction. Regarding the problem of angioedema resulting from candesartan intake, it is crucial for physicians to be wary of prescribing ARBs and to pay particular attention to patient's previous history of angioedema, predisposition to allergies and all possible drug interactions when it comes to diagnosis of swollen tongue, oral floor, and/or throat.

Conflict of interest
None

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