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PRIKAZ SLUČAJA
CASE REPORT

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Oralna bulozna erupcija uzrokovana azitromicinom

Bullous Oral Eruptions Caused by Azithromycin

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Sažetak
Makrolidi se smatraju najsigurnijom skupinom antibiotika i imaju vrlo nisku učestalost alergijskih reakcija (0,4 do 3 %). Opisali smo slučaj mladog pacijenta kod kojega se razvila bulozna erupcija na obraznoj sluznici i usnama nakon ingestije treće doze azitromicina. Nakon terapije kortikosteroidima lezije su se počele povlačiti, ali četvrti dan pojavila se na sluznici usne šupljine nova bulozna erupcija slabijeg intenziteta. To se može objasniti dugim vremenom poluraspada azitromicina u plazmi. Naime, taj se lijek može otkriti u lizatu neutrofila 28 dana nakon posljednje doze, što može biti povezano s većim rizikom od popratnih pojava. Prema našim spoznajama i dostupnim podacima iz literature, to je prvi opisani slučaj oralne erupcije u tijeku liječenja azitromicinom. Unatoč činjenici da azitromicin ostaje jedan od makrolida koji se najbolje toleriraju, ponekad može prouzročiti ozbiljne nuspojave.

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Uvod

Makrolidi se smatraju najsigurnijom skupinom antibiotika – učestalost alergijskih reakcija je od 0,4 do 3 posto (1). Azitromicin, jedan od makrolidnih antibiotika, ima nekoliko jedinstvenih farmakokinetičkih svojstava koja omogućuju kratak terapijski režim zahvaljujući njegovu duljem vremenu poluraspada (više od 40 sati) i širokom antibakterijskom spektru (2). Ipak, uočene su mnogobrojne popratne pojave (3). Pretraživanjem baze podataka MEDLINE u razdoblju od 1993. do 2009., pronašli smo pedeset članaka u kojima su opisani slučajevi nuspojava nakon liječenja azitromicinom, uključujući akutni i rekurentni intersticijski nefritis (4), ototoksičnost (5), kožne lezije izazvane istodobnom primjenom više lijekova (6), vaskulitis (7), hepatotoksičnost (8), srčane simptome (9), katatonične simptome (10), preosjetljivost zbog profesionalne izloženosti lijeku i kontaktni dermatitis (11) te rekurentni herpes simpleks rožnice (12). U većini slučajeva dijagnoza alergije bila je postavljena nakon što su isključeni ostali mogući uzroci te preklapanja vremena uzimanja lijeka i pojave reakcije, a ne izravnim alergološkim testiranjem.

Prikazali smo slučaj mladog pacijenta u kojeg se razvila bulozna erupcija na obraznoj sluznici i usnama nakon treće doze azitromicina.

Introduction

Macrolides are considered the safest group of antibiotics, with the allergy prevalence of 0.4-3% (1). Azithromycin, one of the macrolide antibiotics, has several unique pharmacokinetic properties that provide short-course therapeutic regimens due to its long elimination half-life (over 40 h) and wide antibacterial spectrum (2). Nevertheless, a number of side effects have been described (3). By searching the MEDLINE database in the period of 1993 to 2009, we identified fifty articles describing cases of adverse effects of azithromycin including acute and recurrent interstitial nephritis (4), ototoxicity (5), multidrug-induced cutaneous lesions (6), vasculitis (7), hepatotoxicity (8), cardiac symptoms (9), catatonic symptoms (10), occupational hypersensitivity and contact dermatitis (11) and recurrence of herpes simplex keratitis (12). In majority of reported cases, the diagnosis of allergy was based more on exclusion of other possible causes and overlapping at the time of drug intake and the occurrence of drug reaction than on allergy testing.

We present a case of a young patient who developed bullous eruption on the oral mucosa and lips after ingestion of the third dose of azithromycin.

Prikaz slučaja

Dječak od 13 i pol godina upućen je u našu ustanovu od dermatologa zbog intraoralne boli i bulozne erupcije na sluznici usta koja se dogodila preko noći. Kožnih lezija nije bilo. Pacijent je upravo bio završio trodnevno liječenje azitromicinom u dozi od 500 mg na dan zbog infekcije gornjih dišnih putova. Druge lijekove nije uzimao. Drugog dana liječenja primijetio je jednu ulceraciju u ustima. Nakon treće doze azitromicina na obraznoj sluznici u području malih slinovnica pojavilo se više visećih buloznih promjena, što je otežalo uzimanje hrane (slike 1a,1b,1c).

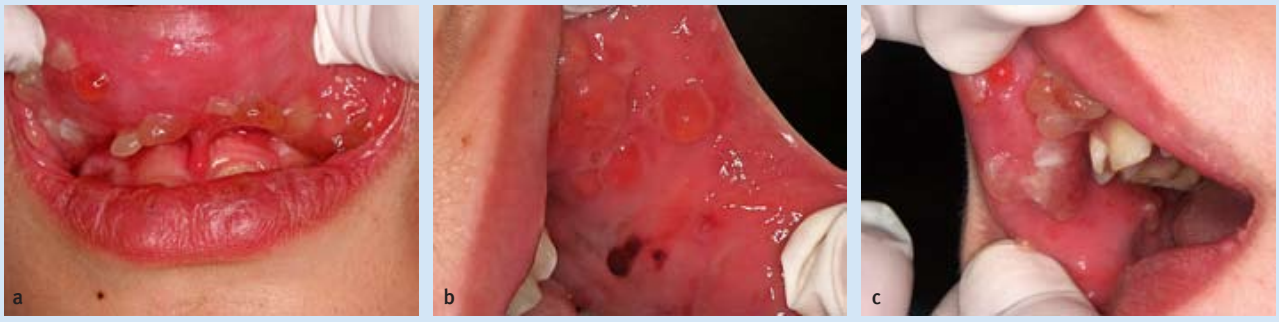
U osobnoj anamnezi pacijenta majka dječaka navela je nespecifičnu reakciju na čepiće diklofenaka u ranom djetinjstvu i korištenje različitih antibiotika (cefalosporina i penicilina), pa čak dva puta i azitromicina, no bez ikakve reakcije. U obiteljskoj anamnezi majka je navela da je imala Quinckeov edem u dobi od 13 godina i Stevens–Johnsonov sindrom na sulfonamide prošle godine. Majka dječaka je također rekla da drugi sin i brat pacijenta pati od bronhitisa i astme.

Pacijent je imao nalaz kompletne krvne slike prije nego što je počeo uzimati azitromicin i analiza je pokazala blagi rast neutrofila (56,9 %), monocita (13,1 %) i eozinofila (8,1 %), a ostali su krvni parametri bili unutar referentnih vrijednosti. Druge laboratorijske pretrage nisu rađene.

Pri kliničkom pregledu otkriven je opsežni bulozni osip na obraznoj sluznici samo u području malih žlijezda slinovnica. Bule su bile ispunjene seroznim i hemoragičnim sadržajem. Biopsija nije rađena. Propisan mu je sistemski metilprednizolon u početnoj dnevnoj dozi od 40 miligrama, a količina se postupno smanjivala svaka dva dana za osam miligrama. Nakon dva dana liječenja kortikosteroidima lezije su počele regredirati, ali četvrti dan pacijent je prijavio novu buloznu erupciju slabijeg intenziteta na sluznici bez općih simptoma. Početna visoka doza steroida postupno je snižavana tijekom dva tjedna prije nego što je prekinuto uzimanje lijeka. Na kontrolnom pregledu mjesec dana kasnije bolesniku je predloženo alergološko testiranje ('patch' test (13) i test CAST ELISA), što on nije učinio. U skladu s nacionalnim propisom prema kojemu se svaku nuspojavu na lijek mora prijaviti Agenciji za lijekove i medicinske proizvode RH, ta je reakcija prijavljena kao popratna pojava na azitromicin.

Case report

A 13.5-year-old boy was referred to our Department by a dermatologist due to intra-oral pain and bullous eruption on the oral mucosa which occurred overnight. No cutaneous lesions were present. The patient had just finished his three-day treatment with azithromycin in the dose of one 500 mg tablet per day due to an upper respiratory tract infection. No other therapy was prescribed. During the second day of treatment, the patient noticed an ulceration in his mouth. After the third dose of azithromycin, multiple hanging bullous changes appeared on his buccal mucosa in the region of minor salivary glands, which interfered with his masticatory function (Fig.1a, 1b, 1c).



Slika 1a-c. Oralni nalaz prvog dana erupcije
Figure 1a-c Oral findings on the first day of the eruption.

His medical history revealed a non-specific reaction to diclofenac suppositories in the early childhood. The use of various antibiotics since then (cephalosporins and penicillins) and even azithromycin twice before was without any reactions. The patient's family history revealed that his mother had experienced Quincke edema when she was 13 years old and Stevens Johnson syndrome as a reaction to sulphonamides the previous year. The mother also reported that the patient's brother suffers from bronchitis and asthma.

The patient had a complete blood count test done before he started taking azithromycin and the findings revealed a slight increase in neutrophils (56,9%), monocytes (13,1%) and eosinophils (8,1%), while the other blood test results were normal. No other laboratory tests were done.

Clinical examination revealed extensive bullous enanthema on oral buccal mucosa, only in the region of minor salivary glands. Bullae were filled with serous and hemorrhagic content. The patient did not consent to a biopsy. Systemic methylprednisolone was prescribed in the starting single daily dose of 40 mg and gradually reduced to 8 mg every two days. After two days of steroid therapy the lesions started to regress, but on the fourth day, the patient reported a new bullous eruption on the oral mucosa with lower intensity and without general symptoms. The initial high dose of steroids was gradually tapered off over the course of two weeks before the complete withdrawal of the medication. At the control examination one month later, the patient was referred to allergy testing ('patch' test (13) and CAST ELISA test), which he has not done. In accordance with the national law regu-

Rasprava

Antibiotici općenito, a osobito penicilini i sulfonamidi, uzročnici su velikog broja alergijskih reakcija na lijekove. Dijagnoza alergije na antibiotike rijetko je jasna i detaljna, često je najvažnija anamneza o nastanku neželjenih reakcija u vrijeme uzimanja lijeka. Naime, nema jedinstvenoga testa za alergiju na antibiotike. Osnovni problem u dijagnostici alergije na antibiotike imunološkim metodama jest činjenica da velik dio antibiotika nisu potpuni antigeni nego haptenski metaboliti roditeljskog lijeka u kombinaciji s tkivnim prijenosnim proteinima. Osim penicilina, rijetko su identificirani imunoreaktivni metaboliti lijekova.

U dokazivanju alergijske reakcije mogu se primijeniti obje vrste testova – kožni testovi i određivanje alergenski specifičnog IgE-a iz krvi pacijenta (test RAST). RAST test je manje osjetljiv i skup je, te se općenito rabi samo za pacijente kod kojih se ne mogu obaviti kožni testovi. Tim se testovima određuje preosjetljivost na određene antibiotike, ponajprije na penicilin, ali su od pomoći samo u predviđanju reakcije posredovane IgE protutijelima. Kožna testiranja obavljaju samo stručnjaci zbog rizika od anafilaksije kod bolesnika s ekstremnom alergijom na antibiotike. Pacijenti koji su imali makulopapularni osip (čest je kod djece) najčešće imaju negativan kožni test (14). Ako su kožni testovi pozitivni, pacijent je alergičan na penicilin, a ako su negativni nalaz negira alergiju na penicilin, ali je ne isključuje u cijelosti. Moguće je da imuni odgovor usmjeren prema metabolitima lijeka možda nije posredovan IgE protutijelima ili je jednostavno proteklo previše vremena od nastanka nuspojave. Prema mišljenju Brockowa i suradnika (15), testiranje treba obaviti najranije tri tjedna nakon razvoja popratne pojave, ali ne kasnije od nekoliko mjeseci. Provokacijski test smatra se najsigurnijim jer se radi u kontroliranim bolničkim uvjetima. No, to se preporučuje samo ako je osobi potreban određeni antibiotik, a drugi antibiotici nisu dostupni. Vjerojatnost alergije vrlo je mala. Ako je mogućnost alergije visoka, općenito se preporučuje desenzibilizacija (16).

Na temelju kliničke slike lezija kod našeg pacijenta, diferencijalna dijagnoza uključila je multiformni eritem, bulozni pemfigoid, ožiljkasti pemfigoid ili rani Stevens – Johnsonov sindrom. Kronična bulozna bolest djece (KBBD), iako rijetka, također se razmatrala, ali nedostajali su klinički kriteriji kao što su mlađa dob i zahvaćenost ostalih sluznica.

Kako bi se isključile ili potvrdile te dijagnoze, obično se uzima biopsijski uzorak za patohistološku analizu i izravnu imunofluorescenciju. No, kod našeg pacijenta biopsija nije učinjena zbog nekoliko razloga – nije bilo suglasnosti zbog pacijentova teškog lokalnog nalaza i opsežnosti oralnih lezija, lošeg općeg stanja i dobi, obiteljske anamneze alergijskih reakcija te kronološke podudarnosti između uzimanja lijeka i pojave simptoma. Patohistološki nalaz, kao dokaz alergijske reakcije, nije specifičan i obično pokazuje leukotoksični va-

lation under which any side effects of the drug must be reported to the Agency for Medicinal Products and Medical Devices, this reaction was reported as a side effect of azythromycin.

Discussion

In general, antibiotics, particularly penicillins and sulfonamides, account for a large proportion of allergic drug reactions. The diagnosis of antibiotic allergy is rarely clear-cut and the history of the events surrounding the onset of the adverse reaction is very important. There is no single test for antibiotic allergy. A basic problem in diagnosing antibiotic allergy by immunological methods lies in the fact that most antibiotics are not complete antigens but rather haptenic metabolites of the parent drug coupled with a carrier tissue protein. With the exception of penicillin, the immunoreactive drug metabolites have rarely been identified. Both skin tests and allergen specific IgE (RAST) test can be carried out. RAST test is less sensitive and expensive, and, in general, should only be used for patients who cannot be skin tested. Skin testing is of definite value in assessing hypersensitivity to certain antibiotics, primarily penicillin, but is only helpful in predicting reactions caused by IgE antibodies. Skin testing should only be performed by specialists due to the risk of anaphylaxis in patients with extreme antibiotic allergy. Patients who have had a maculopapular rash (common in children) usually have negative skin test results (14). If the skin tests are positive, the patient is allergic to penicillin but if the skin tests are negative, the results are strongly against penicillin allergy but do not rule it out completely. It is possible that the immune response is directed towards drug metabolites, and may not be mediated by IgE antibodies or simply too much time has elapsed from the occurrence of side effects. According to Brockow et al. (15), testing should be done not earlier than three weeks after the development of side effects and no later than a few months. Oral challenge is considered safest because it is done in an office setting. However, this is only recommended if the person requires particular antibiotic and no other antibiotic is available and the chances of a true allergy are small. If the chances of a true allergy are high, desensitization is generally recommended (16).

Based on clinical appearance of lesions in our patient, the differential diagnosis included bullous diseases such as pemphigus vulgaris, linear IgA disease, bullous erythema multiforme, bullous pemphigoid, cicatricial pemphigoid or early Stevens Johnson's syndrome. Chronic bullous disease in children (CBDC), although rare, was also considered but clinical criteria such as patient age and affection of other mucous membranes were lacking.

For exclusion or confirmation of these diagnoses, a biopsy is usually taken for histopathologic examination and for direct immunofluorescent test. However, the biopsy was not done in this case because of several reasons: lack of consent to carry out the biopsy due to patient's severe local finding and extensiveness of oral lesions, poor general condition and the patient's young age; family history of allergic reactions; chronological coincidence between taking the medica-

skulitis koji može imati i druge uzroke (17). No, čak ako su nalazi i neuvjerljivi, oni pomažu jer mogu biti mjerilo za isključenje kako bi se potvrdila klinička dijagnoza. Serologija na infekciju HSV-om također nije rađena jer se protutijela za potvrdu dijagnoze primarne infekcije HSV-om počinju pojavljivati unutar tjedan dana i dosežu vrhunac u razdoblju od tri tjedna. Čak i pozitivan nalaz virusa Herpes simplex na sluznici usne šupljine ne mora nužno značiti da je uzrokovao lezije (17).

Dijagnoza (suspektne) preosjetljivosti na lijekove treba biti postavljena na temelju detaljne kliničke anamneze i fizikalnog pregleda, a zatim slijedi jedan ili više postupaka – kožni testovi kada su dostupni i izvedivi, laboratorijski testovi te provokacijski testovi (18). Svaki od njih ima nekih ograničenja. Premda u našem slučaju pacijent nije otišao na preporučeno alergološko testiranje, Agencija za lijekove i medicinske proizvode RH prijavljenu je nuspojavu označila kao očekivanu reakciju preosjetljivosti i nuspojavu tipa B na azitromicin.

Učestalost nuspojava tipa B varira između 0,01 i 0,1 posto, što se smatra rijetkom popratnom pojavom. U tom slučaju potrebno je upozoriti bolesnike da prestanu uzimati lijek. Za postavljanje dijagnoze preosjetljivosti u tim slučajevima preporučuje se patch test (15) sa sumnjivim lijekom. Budući da je reakcija kod našeg pacijenta završila nakon desetak dana, ocijenjeno je da je to u skladu s farmakodinamičkim profilom azitromicina koji ostaje u terapijskim koncentracijama približno10 dana. Prema podatcima iz literature, pogoršanje kliničke slike nakon početne regresije kliničkih simptoma tijekom terapije steroidima može se objasniti time da azitromicin ima vrijeme poluraspada u plazmi dulje od 40 sati (2), a prema nekim autorima čak i 60 sati (19,20) te se može naći u lizatu neutrofila 28 dana nakon posljednje doze, što može biti povezano s većim rizikom od neželjenih učinaka (2).

Klinički farmakolog sugerirao je moguću reakciju preosjetljivosti na azitromicin i izbjegavanje daljnjeg korištenja makrolida.

Prema našim spoznajama i podatcima dostupnima iz literature, to je prvi opisani slučaj oralne erupcije nakon liječenja azitromicinom.

U dosadašnjim dokazima iz literature ističe se kako nije vjerojatno da alergija na makrolide obuhvaća cijeli razred lijekova. Ako je to točno, izbjegavanje može biti ograničeno na pojedini makrolidni uzročnik (1,21). Izbjegavanje lijeka je terapija izbora, dok se desenzibilizacija pokazala uspješnom u nekoliko slučajeva (21). Zbog dužeg vremena poluraspada u plazmi, liječenje azitromicinom može biti povezano s većim rizikom od neželjenih učinaka (2). Unatoč činjenici da azitromicin ostaje jedan od najbolje toleriranih makrolida (22), ponekad može biti ozbiljnih nuspojava.

tion and the occurrence of symptoms. Histology as a proof of allergic reaction is not specific and usually shows leukotoxic vasculitis which may have other causes (17). However, even if the results are inconclusive, they can serve as an exclusion criterion to strengthen clinical diagnosis. Serology on HSV infection was not performed because antibodies to HSV in acute viral disease begin to appear in a week and reach a peak in three weeks for the confirmation of diagnosis of primary HSV infection. Even a positive finding of HSV in oral lesions would not necessarily mean that HSV caused the lesion (17).

A diagnosis of (suspected) drug hypersensitivity should be established based on a detailed clinical history and a physical examination, followed by one or more of the following procedures: skin tests when available and validated, laboratory tests, and ultimately, provocation tests (18). Each of the tests has some limitations, as explained previously. In our case the patient has not done the recommended allergy testing. According to the Agency for Medicinal Products and Medical Devices, the reported side effect is indicated as expected. This was most probably a reaction of hypersensitivity, adverse effect of type B. The frequency of these side effects varies between 0.01% and 0.1%, which is considered a rare side effect. In this case, it is necessary to warn patients to stop taking the drug any further. For establishing the diagnosis of hypersensitivity in these cases, it is recommended to do a patch test (15) with the suspected drug. Since the reaction in our patient ended after approximately 10 days, it is suggested that this is consistent with the pharmacodynamic profile of azithromycin, which remains at therapeutic concentrations during approximately 10 days. According to data from the literature, deterioration of clinical picture after initial regression of clinical symptoms during steroid therapy could be explained by the finding that azithromycin has a plasma half-life of over 40 h (2), according to some authors even 60h (19, 20) and is detectable in neutrophil lysates 28 days after the last dose, which may be related to the higher risk of adverse effects (2).

A clinical pharmacologist suggested a possible hypersensitivity reaction to azithromycin and avoidance of further use of macrolides.

To our knowledge and from the available literature, this is the first described case of oral eruption after azithromycin treatment.

Evidence from the literature so far point out that macrolide allergies are unlikely to be class allergies. If this is correct, eviction could be limited to the single causal macrolide (1, 21). Eviction is the treatment of choice, while desensitization proved to be successful in a few cases (21). Due to its longer plasma half-life, treatment with azithromycin may be related to the higher risk of adverse effects (2). In spite of the fact that azithromycin remains one of the best tolerated macrolides (22), potentially severe adverse reactions may sometimes occur.

Abstract
Macrolides are considered the safest group of antibiotics, with a very low prevalence of allergic reactions (0.4-3%). We present a case report of a young patient who developed bullous eruption on buccal mucosa and lips after ingestion of the third dose of azithromycin. After taking steroid therapy the lesions started to regress, but on the fourth day a new bullous eruption appeared on labial mucosa with lower intensity. This could be explained by the fact that azithromycin has a long plasma half-life and is detectable in neutrophil lysates 28 days after the last dose, which may be related to a higher risk of adverse effects. According to our knowledge and from the available literature. This is the first described case of oral eruption after azithromycin treatment. In spite of the fact that azithromycin remains one of the best tolerated macrolides, potentially severe adverse reactions may sometimes occur.

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Key words
Macrolides; Azithromycin; Hypersensitivity; Mouth Mucosa; Blister

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