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Štetni učinci antiepileptika lamotrigina s oralnim implikacijama: prikaz slučaja

Adverse Effects of Antiepileptic Drug Lamotrigine and Oral Implications: Case Report

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Sažetak

Opisan je slučaj pacijentice s kliničkom slikom opsežnih oralnih lezija nakon što je počela s terapijom *Lamotriginom*. Kliničkom slikom dominirale su bilateralna facijalna otekline i otekline mentalnog prostora s aktivno secernirajućom ekstraoralnom fistulom u središnjem području brade. Doktori dentalne medicine trebali bi biti svjesni rizika povezanih s ovim lijekom te bi trebali uočiti rizičnu populaciju među pacijentima koji boluju od epilepsije, bipolarnog poremećaja i neuroloških poremećaja.

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Ključne riječi

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Uvod

Lamotrigin je antiepileptik koji se koristi u terapiji parcijalnih ili generaliziranih kloničko-toničkih napadaja. U posljednjih nekoliko godina njegova se uporaba povećala (1, 2) i to zato što se taj lijek, uz ostale antiepileptike, propisuje u slučaju bipolarnog poremećaja i neuroloških poremećaja (2). Posljedica je povećan rizik od pojedinih mukokutanih bolesti u populaciji pacijenata koji primaju takvu terapiju. Među štetnim učincima toga lijeka su razmjerno česti makulopapularni osipi (3–15%), a najteže štetno djeluje na nastanak potencijalno smrtonosnog Stevens–Johnsonova sindroma i toksičnu epidermalnu nekrolizu (2, 3, 4, 5). Štetni učinci češći su tijekom prva dva mjeseca terapije, te u slučaju da se doza naglo poveća ili se lijek propisuje zajedno s valproatom (4, 6).

Zaposleni u sustavu zdravstvene zaštite, uključujući i doktore dentalne medicine, trebali bi biti svjesni rizika povezanih s ovim lijekovima te bi trebali uočiti posebno ugroženu populaciju.

Introduction

Lamotrigine is an antiepileptic medication used in the treatment of partial and generalized tonic-clonic seizures. The use of lamotrigine has increased in the past years (1, 2). This happens because lamotrigine is, along with other antiepileptic drugs, used in the treatment of bipolar disorder and neurologic disorders (2). The use of lamotrigine increases the risk of some mucocutaneous disorders in the population of patients receiving lamotrigine therapy. Among adverse reactions, maculopapular rashes are relatively common (3–15%), and the most serious adverse effect of lamotrigine is development of potentially fatal Stevens–Johnson syndrome and toxic epidermal necrolysis (2,3,4,5). Adverse reactions are more common during the first two months of treatment with lamotrigine, if the dosage is increased too rapidly, and if valproate is co-administered (4,6).

Thus, health care professionals, including dental medicine professionals, should be aware of risks involved with using these drugs, and should recognize the population which is particularly at such a risk.

U ovom članku opisan je slučaj pacijentice s kliničkom slikom opsežnih oralnih lezija (pseudomembranozne, papulozne, bulozne i erozivne) nakon početka terapije *Lamotriginom*.

Prikaz slučaja

Tridesetpetogodišnja žena upućena je u Zavod za endonciju i restaurativnu stomatologiju Stomatološkog fakulteta Sveučilišta u Zagrebu radi endodontskog liječenja dva zuba – 42 i 41. Kliničkom slikom dominirala je obostrana facijalna oteklina i oteklina mentalnog prostora s aktivno secernirajućom ekstraoralnom fistulom u središnjem području brade. Poslana je iz Zavoda za oralnu medicinu Stomatološkog fakulteta Sveučilišta u Zagrebu, gdje je ranije bila mjesec i pol liječena zbog lezija na oralnoj sluznici (sublingvalnoj, palatinalnoj, bukalnoj) otopinom *D-Panthenola* i kapima *Garasone*. Razmatrana je i mogućnost sialolitijaze koja je nakon radiološkog nalaza isključena kao uzrok oteklina lica. U tom je trenutku dijagnoza specijalista oralne medicine bila *ulceratio mucosae oris i sialolithiasis in observationem*.

Specijalist oralne medicine sugerirao je da bi oralne manifestacije mogle biti posljedica štetnog učinka lijeka *Lamotrigina*, no u tom trenutku neuropsihijatrijska terapija nije bila promijenjena.

Na rendgenskoj snimci mandibularnih sjekutića bila je vidljiva ekstenzivna periradikularna transparentija oko zuba 42 i 41 (slika 1.). Na bukalnoj sluznici bile su erozivne lezije, a na sublingvalnoj pseudomembranozne (slika 2.). Medicinska anamneza otkrila je da pacijentica boluje od autizma i prirodene srčane greške (ventrikulo-septalni defekt), a neuropsihijatar je propisao terapiju *Zoloftom* (sertralina) i *Lamalom* (lamotrigin).

Provedeno je endodontsko liječenje zuba 42 i 41. Tijekom sljedećeg posjeta nakon 10 dana, ekstraoralna fistula pokazivala je znakove cijeljenja. Na mjestu cijeljenja ekstraoralnog otvora fistule bio je lagani konkavitet, no još je postojala oteklina mentalnog prostora te facijalnih prostora (slika 3.). Intraoralni nalaz i simptomi su se pogoršali. Na sluznici obraza i donje usne pojavile su se opsežne erozivne lezije (slika 4.). Pacijentica se žalila na bol, osjećaj pečenja i svrbeža te ujutro na žućkasti sekret. Kontrolni CBCT otkrio je opsežan gubitak kosti u području zuba 42 i 41 (slika 5.). Prikazan je sinusni trakt – gnojni eksudat probio je bukalni (vestibularni) korteks.

Terapija *Lamotriginom* je ukinuta.

Nakon tjedan dana oteklina se značajno smanjila, lezije na sluznici obraza su cijelile (slika 6.), a pseudomembranozne oteklinae na donjoj usni također su se smanjile (slika 7.).

Pacijentica je upućena u Zavod za oralnu medicinu radi daljnjeg praćenja.

Rasprava

Kad je pacijentica primljena na liječenje, izvor infekcije mentalnog prostora bili su donji sjekutići koji su bili otvoreni tri mjeseca. Svrha endodontske terapije u tom je trenutku bila očistiti i obturirati kompromitirane zube. Ostaje upitno jesu li ti zubi uopće trebali biti trepanirani i endodontski liječeni. Štetni učinci *Lamotrigina* protumačeni su kao odontogeni

This article describes the case of a patient who presented with extensive oral lesions: (pseudomembranous, papulous, bullous and erosive) after starting treatment with lamotrigine.

Case report

A 35-year old woman was referred to the Department of Endodontics and Restorative Dentistry, School of Dental Medicine, University of Zagreb, for endodontic treatment of teeth 42 and 41. The patient presented with bilateral facial swellings and mental space swelling with actively draining extra oral sinus tract in the central chin area. She was referred from the Department of Oral Medicine, School of Dental Medicine, University of Zagreb, where she had been treated for oral mucosa lesions (sublingual, palatal, buccal) with D-Panthenol solution and Garasone gtt for the past month and a half. Sialolithiasis was also considered, and upon radiologic examination it was excluded as the cause of facial swelling. At that stage the diagnosis of oral medicine specialist was apthous like ulcerations and sialolithiasis *in observationem*.

Oral medicine specialist suggested that such oral manifestations could be adverse effects of lamotrigine drug, but at that stage, neuropsychiatric therapy was not changed.

A radiograph of mandibular incisors revealed extensive periradicular radiolucency around teeth 42 and 41 (Figure 1.). Erosive lesions could be seen on buccal mucosa and pseudomembranous lesions on sublingual mucosa (Figure 2.). Medical history revealed autism, congenital heart malformation (ventricular-septal defect), Zoloft (*sertralinum*) and Lamal (lamotrigine) was prescribed by a neuropsychiatrist.

Endodontic treatment of teeth 42 and 41 was performed. At next appointment, after 10 days, the extra oral sinus tract showed signs of healing. Slight concavity of the skin was present in the area of the healing extra oral opening. Nevertheless, the mental swelling remained, as well as bilateral buccal space swellings (Figure 3). Intraoral signs and symptoms got worse. The buccal mucosa and lower lip mucosa presented with extensive erosive lesions (Figure 4). The patient complained about pain, burning, itching and a yellowish-watery discharge in the early morning hours. Control cone beam CT revealed extensive bone loss in 42, 41 region (Figure 5). The sinus tract was visualized: the purulent exudate has broken through the overlying cortical plate.

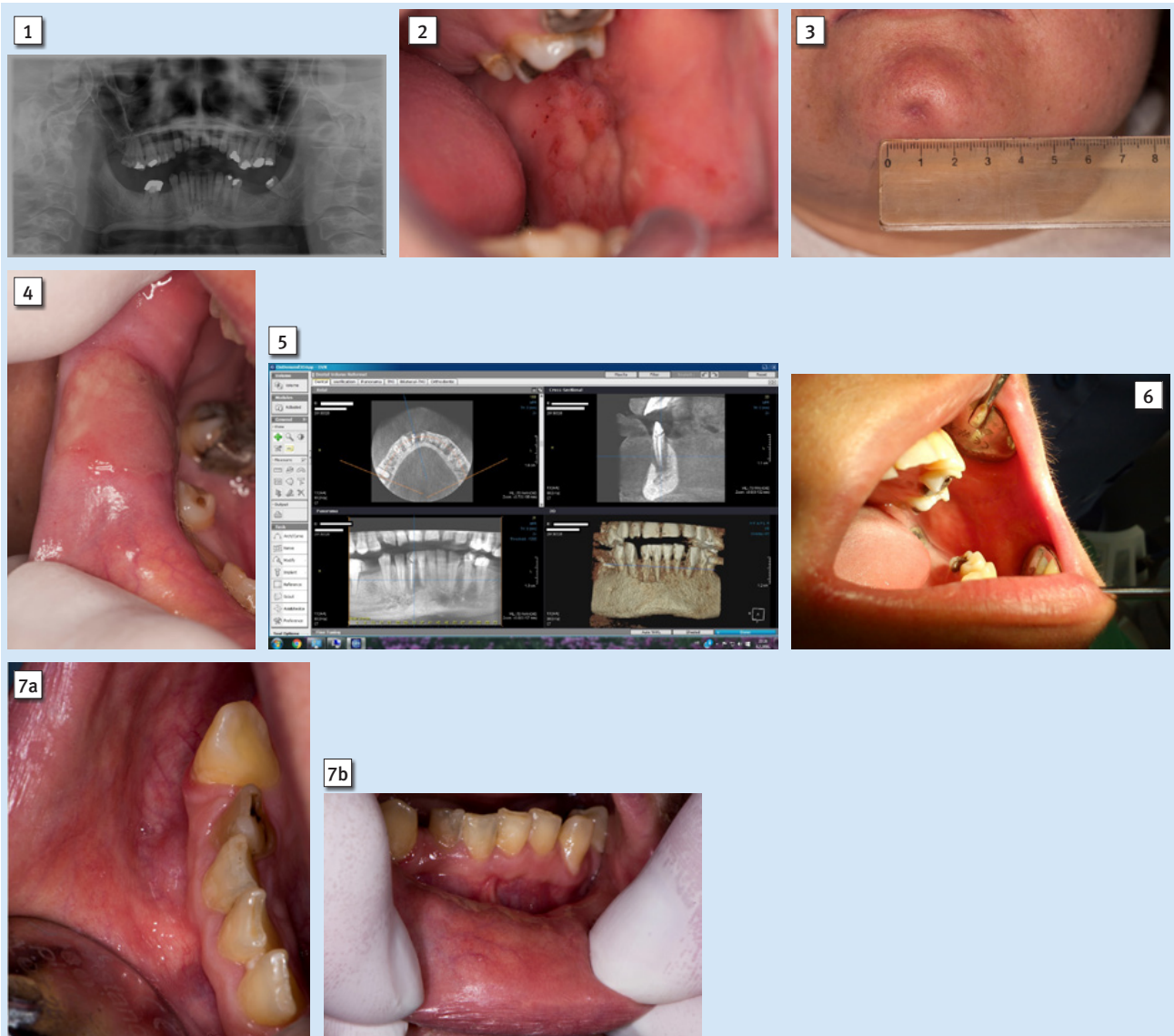
Lamotrigine was withdrawn from the patient's therapy.

After one week, the swellings decreased, buccal lesions were healing (Figure 6), and pseudomembranous lesion at the lower lip mucosa decreased (Figure 7).

The patient was referred to the Department of Oral Medicine for follow up of oral mucosa lesions.

Discussion

Lower incisors, which were left open for a period of three months, were a source of infection of mental space. The aim of endodontic therapy at that point was to clean, shape and obturate the compromised teeth. The question remains whether those teeth were endodontic treatment candidates in the first place. The adverse effects of lamotrigine were in-



- Slika 1.** Digitalni ortopantomogram učinjen prije endodontskog tretmana; može se vidjeti transparentija u području zuba 41 i 42 (strjelice)
Figure 1 Digital panoramic radiograph made before endodontic treatment. A radiolucent lesion in the region 41, 42 can be seen (arrows)
- Slika 2.** Opsežna erozivna lezija na bukalnoj sluznici
Figure 2 Extensive erosive lesions on buccal mucosa
- Slika 3.** Fistula pokazuje znakove cijeljenja 10 dana nakon endodontske terapije; vidljiva je oteklina mentalnog i bukalnih prostora
Figure 3 Sinus tract is showing signs of healing 10 days from endodontic treatment. Mental swelling and bilateral buccal space swellings can be noticed
- Slika 4.** Opsežna erozivna lezija na sluznici donje usnice
Figure 4 Extensive erosive lesions on the lower lip mucosa
- Slika 5.** Postendodontski CB-CT; napunjeni su korijenski kanali zuba 41 i 42; vidi se značajan gubitak kosti oko zuba 41 i 42
Figure 5 Post endodontic CB-CT. Root canals of 41 and 42 are filled. Extensive bone loss is present around teeth 41 and 42
- Slika 6.** Zacijeljene lezije na bukalnoj sluznici nakon prekida terapije *Lamotriginom*
Figure 6 Healed lesions on buccal mucosa after cessation of lamotrigine therapy
- Slika 7a,b.** Zacijeljena sluznica donje usnice nakon prekida terapije *Lamotriginom*
Figure 7a,b Healed lower lip mucosa after withdrawal of lamotrigine therapy

apscesi. Dentalna anamneza otkrila je da su pacijentici tijekom terapije *Lamotriginom* izvađena još tri zuba (45, 47, 37).

Interakcija između *Lamotrigina* i valproata dobro je dokumentirana i kombinacija navedenih lijekova se ne preporučuje (4, 7, 8, 5). Kavitha i suradnici (5) opisali su slučaj pacijenta s bolnim ulkusima u ustima, krvarećim usnicama, osipom po cijelom tijelu i visokom temperaturom od 39 °C (Stevens–Johnsonov sindrom), a uzrok je bila kombinacija *Lamotrigina* i valproične kiseline. No u slučaju naše pacijen-

terpreted as odontogenic abscesses. Dental history revealed that the patient had another three teeth extracted (45,47, 37) while on therapy with lamotrigine.

The interaction between lamotrigine and valproate is well documented, and it is recommended that the two drugs not be combined (4,7,8,5). Kavitha et al. (5) reported on the case of a patient with painful ulcers in the mouth, bleeding lips, rashes throughout the body, and high fever (39°C) induced by a combination of lamotrigine and valproic acid (Stevens–

tice zajedno s *Lamotriginom* bio je propisan i *Sertralin*. Općenito je prihvaćeno da kombinirana terapija s ta dva lijeka ne bi trebala povećati toksični učinak *Lamotrigina* (9). Christensen i njegovi suradnici (9) procjenjivali su farmakokinetičke interakcije između *Sertralina* i *Lamotrigina* te su zaključili da je metabolizam *Lamotrigina*, ako ga pacijenti uzimaju zajedno sa *Sertralinom*, sporiji negoli ako im je ordiniran *Lamotrigin*, ali nisu to smatrali klinički značajnim. No u nekim se studijama sugerira da istodobno uzimanje ova dva lijeka može rezultirati povećanom razinom *Lamotrigina* u krvi i pojavom toksičnih simptoma (10).

Povećana uporaba *Lamotrigina* i ostalih lijekova iz skupine antiepileptika u liječenju psihijatrijskih i neuroloških stanja trebala bi se uzeti u obzir tijekom dentalnog liječenja, a više bi se pozornosti trebalo posvetiti medicinskoj anamnezi.

Zahvala

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Johnson syndrome). This is however not the case with sertraline which was prescribed to our patient. It is generally accepted that combined therapy of lamotrigine with sertraline should not increase the risk of toxic reactions to lamotrigine. Christensen *et al.* (9) evaluated pharmacokinetic interaction between sertraline and lamotrigine, and they concluded that the metabolism of lamotrigine in patients receiving lamotrigine with sertraline was slower compared with those receiving lamotrigine alone, but this was found not to be of clinical significance. Nevertheless, some studies suggest that simultaneous administration of these two drugs could result in elevating lamotrigine blood levels with toxicity symptoms development (10).

Increased use of lamotrigine and other antiepileptic drugs in treating psychiatric and neurological conditions other than epilepsy should be taken into consideration when treating dental patients, and much care should be given to medical history.

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Abstract

We report on a patient who presented with extensive oral lesions. The treatment with lamotrigine is described. The patient presented with bilateral facial swellings and mental space swelling with actively draining extra oral sinus tract in the central chin area. Dental medicine professionals should be aware of the risks involved with using this medication, and should recognize the population at risk among patients suffering from epilepsy, bipolar and neurologic disorders.

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Key words

Anticonvulsants; Oral Lesions; Epilepsy; Bipolar And Related Disorders; Drug-Related Side Effects and Adverse Reactions

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