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

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, buzožne i erozivne) nakon početka terapije Lamotriginom. This article describes the case of a patient who presented with extensive oral lesions: (pseudomembranous, populous, bullos and erosive) after starting treatment with lamotrigine.

Prikaz slučaja
Tridesetpetogodišnja žena upućena je u Zavod za endodonticu 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 ekstroarhalnom fistulom u središnjem području brade. Poslana je iz Zavoda za oralnu medicinu Stomatološkog fakulteta Sveučilišta u Zagrebu, gdje je ranije bila mjesec i pol liječenja zbog lezija na oralnoj služnici (sublingvalnoj, palatinalnoj, bukojalnoj) otopinom D-Panthenola i kapima Garasone. Razmatrana je i mogućnost sijalolitijaze koja je nakon radiološkog nalaza isključena kao uzrok oteklinice lica. U tom je trenutku dijagnoza pacijentice sugerirao odontogeni komponent.

Pacijentica se žalila na bol, osjećaj pečenja i svrbeža te ujutro za i donje usne pojavile su se opsežne erozivne lezije (slika 4.). Intraoralni nalaz i simptomi su se pogoršali. Na sluznici optužena su s aktivno secriranjem, a na sublingvalnoj pseudomembranozne (slika 2.). Medical history revealed autism, congenital heart malformation (ventricular-septal defect), Zoloft (sertralinum) i Lamotrigine (lamotrigine). Provedeno je endodontsko liječenje zuba 42 i 41. Tijekom sljedećeg posjeta nakon 10 dana ekstroarhalna fistula pokazivala je znakove cijeljenja. Na mjestu cijeljenja ekstraoralni sljedećim posjetom pojavila se opasnost (slika 6.). Prikazan je sinusni trakt – gnojni eksudat probio je bukojalni (vestibularni) korteks.

Terapija Lamotriginom je ukinuta. Na sublingvalnoj pseudomembranoznoj oteklini na donjoj usni također su se smanjile lezije (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. Svih endodontske terapije u tom je trenutku bila očistiti i obturirati kompromitirane zube. Ostaje upitno je li ti zubi uopće trebali biti trepanirani i endodontski liječeni. Štitni učinci Lamotrigin protumačeni su kao odontogeni.

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 aphthous 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 Lamotrigine (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.

Lamotrign 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—
štetni učinci antiepileptika s oralnim manifestacijama
Ivanišević Malčić i sur.

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–Johnsonov sindrom), a case in which the patient showed signs of healing 10 days after the endodontic treatment. The mental swelling and bilateral buccal space swellings can be noticed.

Slika 1. Digital ortopantomogram učinjen prije endodontskog tretmana; može se vidjeti transparentacija u području zuba 41 i 42 (strijelice)

Figure 1 Digital panoramic radiograph made before endodontic treatment. A radiolucent lesion in the region 41, 42 can be seen (arrows)

Slika 2. Opša erozivna ležija 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. Opša erozivna ležija 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 ležije 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
tice zajedno s lamotriginom bio je propisan i sertralin. Općenito je prihvaćeno da kombiniranaja terapija s ta dva lijeka ne bi trebala povećati toksični učinak lamotrigin (9). Christensen i njegovi suradnici (9) procjenjavali su farmakokinetičke interakcije između sertralina i lamotrigina te su zaključili da je metabolizam lamotrigina, ako ga pacijenti uzimaju zajedno sa sertralinem, sporije negoli ako im je ordiniran. Lamotrigin, ali nisu to smatrali klinički značajnim. No u nekim se studijama sugerira da je toksičnost uzimanja ova dva lijeka može rezultirati podražavanjem toksičnosti (10). Povećana uporaba lamotrigina i ostalih lijekova iz skupine antiepileptika u liječenju psychijatrijskih i neuroloških stanja trebala bi se uzeti u obzir tijekom dentalnog liječenja, a više bi se pozornosti trebalo posvetiti medicinskoj anamnezi.

Zahvala
Ovaj prikaz slučaja dio je znanstvenog projekta Ministarstva znanosti, tehnologije i sporta Republike Hrvatske Br. 665-0650445-0434.

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.

Acknowledgements
This report has been made as part of scientific project No. 665-0650445-0434 supported by the Ministry of Science, Education and Sports, Republic of Croatia.

References
1. Varghese SP, Haith LR, Patton ML, Guilday RE, Ackerman BH. Lamotrigine-induced toxic epidermal necrolysis in three patients treated for bipolar disorder. Pharmacotherapy. 2006 May;26(5):699-704.
2. Sladden M, Mortimer N, Chave T. Toxic epidermal caused by lamotrigine. Aust Fam Physician. 2004 Oct;33(10):829-30.
3. Chaffin JJ, Davis SM. Suspected lamotrigine induced toxic epidermal necrolysis. Ann Pharmacother. 1997 Jun;31(6):720-3.
4. Yalcin B, Karaduman A. Stevens-Johnson syndrome associated with concomitant use of lamotrigine and valproic acid. J Am Acad Dermatol. 2000 Nov;43(5 Pt 2):898-9.
5. Kavitha S, Anbuchelvan T, Mahalakshmi V, Sathyra R, Sabarinath TR, Gururaj N, et al. Stevens–Johnson syndrome induced by a combination of lamotrigine and valproic acid. J Pharm Bioallied Sci. 2015 Aug;7(Suppl 2):S576-8.
6. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case control study. Lancet. 1999 Jun 26;353(9171):2190-4.
7. Chang CC, Shah IS, Chang HA, Huang SY. Toxic epidermal necrolysis with combination lamotrigine and valproate in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2006 Jan;30(1):147-50.
8. Thome-Souza S, Moreira B, Valente KD. Late adverse effects of the coadministration of valproate and lamotrigine. Pediatr Neurol. 2012 Jul;47(1):47-50.
9. Christensen J, Sandgaard AP, Sidenius P, Linnet K, Licht RW. Lack of interaction between sertraline and lamotrigine in psychiatric patients: a retrospective study. Pharmacopsychiatry. 2012 May;45(3):119-21.
10. Kaufman KR, Gerner R. Lamotrigine toxicity secondary to sertraline. Seizure. 1998 Apr;7(2):163-5.