〔症例報告〕

Treatment of Burning Mouth Syndrome using Anti−Anxiety and Anti−Depressant Drugs : A Case Series.

Durga PAUDEL[1], Masafumi UTSUNOMIYA[1], Koki YOSHIDA[1], Bhoj Raj ADHIKARI[1], Puja NEOPANE[1], Sarita GIRI[2], Jun SATO[1], Hirofumi MATSUOKA[3], Michiko NISHIMURA[1] and Yoshihiro ABIKO[1]

[1]Division of Oral Medicine and Pathology, Department of Human Biology and Pathophysiology, School of Dentistry, Health Sciences University of Hokkaido
[2]Division of Periodontology and Endodontology, Department of Oral Rehabilitation, School of Dentistry, Health Sciences University of Hokkaido
[3]Division of Disease Control and Molecular Epidemiology, Department of Oral Growth and Development, School of Dentistry, Health Sciences University of Hokkaido

Key words : burning mouth syndrome, anti−anxiety drugs, anti−depressants

Abstract

Burning mouth syndrome (BMS) is an intraoral burning or dysaesthetic sensation recurring daily for more than 2 hours per day over more than 3 months without the presence of any clinically evident causative lesions. It occurs predominantly in females during the peri− or post－menopausal period. The etiopathogenesis and treatment of BMS are complex due to its neuropathic and psychological origin. There is no specific treatment protocol for patients with BMS. Anti−anxiety and anti−depressant drugs have been found to be effective in reducing the symptoms of BMS ; however, the appropriate choice of these drugs varies from case to case. Herein, we present a case series of 4 patients with BMS, who received various types of anti−anxiety and anti−depressant medications based on their symptoms. The combination of ethyl loflazepate and milnacipran was effective in case 1 patient. The case 2 patient could not tolerate milnacipran well and was substituted by amitriptyline which reduced pain. The case 3 patient tolerated milnacipran well but was not effective in reducing pain and was substituted by amitriptyline. The case 4 patient did not respond well to various combinations of drug initially but felt comfortable after combination therapy with ethyl loflazepate, venlafaxine and mirtazapine. This report also discusses the rationale behind the use of these drugs.

Introduction

Burning mouth syndrome (BMS) is an intraoral burning or dysaesthetic sensation that recurs daily for more than 2 hours per day over more than 3 months in the absence of any clinically evident causative lesions (International Headache Society, 2018). The neuropathic origin of this condition has been reported in some studies, while others have demonstrated the involvement of psychogenic factors (Galli et al., 2017 ; Jaaskelainen, 2018). The treatment of BMS is complex and varies from the use of topical agents like alpha−lipoic acid and capsaicin, to the ingestion of anti－anxiety and anti−depressant drugs ; in addition, cognitive behavioral therapy has been employed for patients with BMS (de Souza et al., 2018 ; Matsuoka et al., 2017). Studies regarding the judicious use of anti−anxiety and anti−depressant drugs on a case to case basis in patients with BMS are limited (Kremer et al., 2018 ; McMillan et al., 2016). Herein, we present 4 patients with BMS treated with anti−anxiety and anti−depressant drugs.

Case Presentation

Case 1 (*Use of ethyl loflazepate and milnacipran*)

A 78−year−old female visited our clinic with a chief complaint of dull pain in the tongue that began a few months ago. All the secondary causes of burning sensation were ruled out. A psychological assessment test revealed mild anxiety. The pain intensity on the Visual Analog Scale

(VAS) was 70. An initial stage of candidiasis was suspected, and topical application of Amphotericin B (4 ml/day) was prescribed. After a follow−up period of 1 week, the symptoms did not improve and a diagnosis of BMS was reached. An anti−anxiety drug, ethyl loflazepate (0.5 mg/day), was prescribed for the patient. After 2 months of treatment with the drug, the pain had reduced and the VAS score was lowered to 20. The same medication was continued for another 2 months with no change in pain intensity. A serotonin norepinephrine reuptake inhibitor (SNRI), milnacipran (12.5 mg/day) was added to the treatment regime ; the dose was increased to 25 and 50 mg/day during the next 2 months follow−up after reviewing the symptoms. After 6 months, the pain had reduced and the VAS score was further lowered to 10. After another 6 months, the pain had almost disappeared and was limited to a few hours in a month. The patient is on regular follow−up and planning to stop the medication gradually.

Case 2 (*milnacipran intolerance*)

A 53−year−old Japanese female was referred to the Department of Oral Medicine at our university hospital with a chief complaint of burning sensation on the tongue. The dental history revealed that she was treated for temporomandibular disorders (TMD) a year ago and the TMD pain was improving. She complained of generalized burning sensation in the tongue for the past 4 months. The burning sensation was asymptomatic in the morning but gradually increased during the day. She also complained that she did not know where to rest the tongue in the oral cavity. A psychological assessment test revealed mild anxiety, and a VAS score of 80. A diagnosis of BMS was established after the secondary causes of burning mouth were ruled out. Ethyl loflazepate (1 mg/day) was prescribed, and the patient was asked to present at the department after 2 weeks. On her second visit, the patient reported that she was feeling better, and presented with a VAS score of 50. The same medication was continued for about 3 months with a follow−up every month. After 3 months, the symptoms had improved considerably, although they persisted when the patient was stressed. The VAS score during this period was 25. Subsequently, 12.5 mg/day of milnacipran was prescribed to the patient. However, the following week she complained of increased heart rate and blood pressure after taking the drug, and was advised to stop taking the medication. A tricyclic anti−depressant (TCA), amitriptyline (10 mg/day) was prescribed instead. The dosage of the new drug was gradually increased to 20 mg/day and then to 30 mg/day within the next 2 months. After 12 months of treatment, the VAS score was lowered to 5, and the BMS was considerably lower than the tolerance level (limited to 1−2 hours/day). Currently, after 16 months of treatment, the burning sensation is limited to a few days/month, and we are considering decreasing the amitriptyline dose gradually.

Case 3 (*substitution of milnacipran with amitriptyline*)

A 72−year−old Japanese female visited the Department of Oral Medicine of our university hospital with a chief complaint of burning sensation on left side of the tongue for the past few months. Her personal history revealed that she was very active physically and kept herself engaged in sports most of the time. However, the psychological assessment test revealed mild anxiety. The VAS score was measured at 90. After ruling out the secondary causes of the symptoms, a diagnosis of BMS was established. Ethyl loflazepate (1 mg/day) was started, and a reduction in symptoms as well as VAS score (54) was noted after 2 weeks of follow−up. The patient complained of disturbed sleep, so triazolam (0.25 mg/day) was added to the treatment regime for a month. After 2 months of treatment the VAS score was 35. Subsequently, milnacipran (12.5 mg/day) was also prescribed to the patient, and the dose was increased to 25 mg/day the following week after reviewing the symptoms. However, 5 months later, the VAS score remained at 30 ; thus, the patient was asked to take amitriptyline (10 mg/day), instead of milnacipran, with a gradual increased in the dose to 30 mg/day over the next 2 months. After 10 months of treatment, the VAS score was reduced to 10, and another 16 months later, the VAS score was limited to 5. The patient was feeling much better, and plans to taper the dose of amitriptyline.

Case 4 (*combination of ethyl loflazepate, venlafaxine, and mirtazapine*)

A 61−year−old Japanese female visited to our department 4 years back with a chief complaint of burning sensation in the tongue for the past few months. Psychological assessment revealed mild anxiety, and the VAS score was 76. The patient showed no significant improvement in symptoms after a month of ethyl loflazepate (1 mg/day) treatment. After discontinuing the treatment at our hospital for 2 years, the

patient returned with a complaint that her pain had increased (VAS score, 80). After considering her drug history and duration of pain, venlafaxine (SNRI ; 37.5 mg/day) and amitriptyline (10 mg/day) were prescribed, and the patient was advised a weekly follow−up. After 2 months, the pain had subsided and the VAS score was lowered to 5. However, due to a complaint of sticky saliva in the oral cavity, ethyl loflazepate (1 mg/day) was added to the treatment regime. A month later, the pain had increased (VAS score, 30). The dose of amitriptyline was increased to 20 mg/day. After 2 months follow−up, the patient complained of increased pain (VAS score, 50) and dry mouth ; therefore, amitriptyline was stopped and a selective serotonin reuptake inhibitor (SSRI), sertraline (25 mg/day) was started. However, the patient complained of nausea during the next follow−up (1 month) and requested to stop sertraline, and indicated that the combination of venlafaxine, ethyl loflazepate, and amitriptyline worked best for her. The amitriptyline could not be started again because of the occurrence of dry mouth. Thus, mirtazapine (15 mg/day), a noradrenergic and specific serotonergic anti−depressant (NaSSA) was prescribed. The patient felt comfortable during the next appointment and presented with a VAS score of 5. A maxillary and mandibular splint was also prescribed for symptomatic treatment. The patient is on constant follow−up and doing well.

Discussion

BMS is a diagnosis of exclusion, where a diagnosis is reached after all the secondary causes of burning sensation have been excluded. The etiopathogenesis of BMS is complex owing to the two schools of thought with regard to the factors involved ; neuropathic and psychogenic. The nature of chronic pain in BMS resembles the symptoms of neuropathic pain and various studies have provided evidence of the neuropathic origin of this condition (Jaaskelainen, 2018). However, the role of psychological factors has been shown to be equally important (Galli, et al., 2017). BMS patients are interviewed for the presence of underlying psychological factors using psychological assessment tools, such as State−Trait Anxiety Inventory, Diagnostic and Statistical Manual of Mental Disorders or Psychiatry in Primary care (PIPC−Japan, 2018). The patients are referred to a psychiatrist if these assessments indicate the presence of a serious underlying psychological disorder. However, most of the BMS patients have mild stress and anxiety (Galli, et al., 2017). All the cases in this report presented with mild anxiety, and did not need to be referred to psychiatrist. They were prescribed ethyl loflazepate, a potent benzodiazepine, during the first appointment resulting in a reduction in VAS scores in all 4 patients. Benzodiazepines can reduce anxiety and stress by acting on the hypothalamus−pituitary−adrenal axis, which generates pain (Kim & Kho, 2018). In addition, benzodiazepines have an anti−hyperalgesic effect (Vuilleumier et al., 2013). The ethyl loflazepate used in this report may affect both neuropathic and psychological symptoms of BMS. The main advantage of ethyl loflazepate is its non−sedative property and the long elimination time, thereby reducing the incidence of drug dependence (Fukami et al., 2010). These findings indicate that ethyl loflazepate can be a considered as a valid option for the initial treatment of BMS.

Although BMS symptoms were reduced by ethyl loflazepate, the patients complained of residual symptoms. Therefore, anti−depressants including TCA, SSRI, SNRI, and NaSSA were prescribed after initial treatment with ethyl loflazepate (Table 1). The patient in case 1 responded very well to ethyl loflazepate and milnacipran. Milnacipran acts

Table 1 : Clinical presentation and treatment summary of patients

Case	Age/Sex	Clinical presentation	Drugs used	Patient's response	Drug substitution	Effective combination of drugs
1	78/F	Dull pain in tongue since 4 months, mild anxiety, VAS=70	Ethyl loflazepate, Milnacipran	Well tolerated	Not required	Ethyl loflazepate, Milnacipran
2	53/F	Generalized burning sensation in tongue, mild anxiety, VAS=80	Ethyl loflazepate, Milnacipran, Amitriptyline	Increased heart rate and blood pressure due to milnacipran	Milnacipran substituted with amitriptyline	Ethyl loflazepate, Amitriptyline
3	72/F	Burning sensation in left side of tongue, mild anxiety, VAS=90	Ethyl loflazepate, Milnacipran, Amitriptyline	Ethyl loflazepate and milnacipran well tolerated but no reduction in pain	Milnacipran substituted with amitriptyline	Ethyl loflazepate, Amitriptyline
4	61/F	Burning sensation in tongue, mild anxiety, VAS=76	Ethyl loflazepate, Venlafaxine, Amitriptyline, Sertraline, Mirtazapine	Dry mouth due to amitriptyline, Nausea due to sertraline	Amitriptyline substituted with sertraline, Sertraline substituted with mirtazapine	Ethyl loflazepate, venlafaxine and mirtazapine

by inhibiting the reuptake of serotonin and norepinephrine (Welsch et al., 2018), and has been used for patients with BMS (Kato et al., 2011). It is considered as a relatively a safe drug owing to fewer drug interactions and side effects when compared with TCA (Pae, et al., 2009).

In case 2, milnacipran was used after 3 months of ethyl loflazepate monotherapy. However, it was discontinued because the patient complained of increased heart rate and hypertension after taking milnacipran. Milnacipran can also cause nausea, dizziness, hot flashes, and sweating (Xu et al., 2016). Amitriptyline was then used in this patient, and proved effective in reducing the pain. Amitriptyline, a TCA, is commonly used for the treatment of BMS, and acts through various mechanisms (Fenelon et al., 2017). One mechanism involves the antagonistic effect on N−methyl−D−aspartate (NMDA) glutamate receptors, which reduces the sensitization of second order neurons (Watanabe et al., 1993). The other mechanism comprises the inhibition of serotonin, norepinephrine reuptake, and potentiation of endogenous opioid, which act on the descending anti−nociceptive pathway to suppress pain (Dharmshaktu et al., 2012). In some patients, as seen in case 3, milnacipran is well tolerated but not effective in reducing pain. Therefore, milnacipran was stopped and substituted with amitriptyline, which reduced the symptoms in the patient in the current report.

The patient in case 4 had a long history of BMS and did not respond to ethyl loflazepate. Her stress levels were high owing to the long duration of the pain. Combination therapies can be effective in patients who do not demonstrate any reduction in pain after anti−anxiety or anti−depressant monotherapy ; nonetheless, drug interactions should be taken into consideration (Moret, 2005 ; Rojo et al., 2005). A combination of venlafaxine and amitriptyline was prescribed in case 4. Venlafaxine has minimal effect on CYP2D6, and does not alter amitriptyline levels (Gomez Gomez & Teixido Perramon, 2000). The symptoms were reduced within 2 months ; however, the patient presented with symptoms of dry mouth. Amitriptyline is a potent anti−cholinergic drug and can cause dry mouth (Lawson, 2017). It is also known to cause sedation, tachycardia, cardiac arrhythmia, seizure precipitation, and weight gain (Lawson, 2017). Amitriptyline was substituted with sertraline, a SSRI, which acts by inhibiting the reuptake of serotonin into the presynaptic cell and increasing the amount of serotonin in the synaptic cleft (Maina et al., 2002). This can reduce pain, as serotonin plays a role in nociception and mood regulation, and has been shown to be effective in the treatment of BMS (Fleuret et al., 2014). However, the consumption of sertraline resulted in nausea in the patient, and was therefore replaced by mirtazapine, a selective serotonin 2, serotonin 3, and α2−adregenic receptor antagonist. The effects of mirtazapine on chronic pain associated with psychology have been demonstrated previously (Arnold et al., 2008 ; Freynhagen et al., 2006). Eventually, the symptoms had subsided and the condition of the patient was considerably improved. The combination of ethyl loflazepate, venlafaxine, and mirtazapine worked best for this patient. Many BMS patients have admitted that they felt less pain when they had something in their mouth. We used a thin clear thermoplastic splint covering the maxillary and mandibular teeth for this purpose in few patients, as in case 4, which showed good results. The reduction in pain might be because of a placebo effect and must be evaluated in future studies.

Conclusion

The 4 cases presented in this report showed that BMS can be effectively treated by anti−anxiety and anti−depressant drugs. The choice of drug can vary from patient to patient, and the adverse effects of each drug should be well monitored.

References

Arnold P, Vuadens P, Kuntzer T, Gobelet C, & Deriaz O. Mirtazapine decreases the pain feeling in healthy participants. Clin J Pain 24 : 116−119, 2008.

de Souza I F, Marmora B C, Rados P V, & Visioli F. Treatment modalities for burning mouth syndrome : a systematic review. Clin Oral Investig 22 : 1893−1905, 2018.

Dharmshaktu P, Tayal V, & Kalra B S. Efficacy of antidepressants as analgesics : a review. J Clin Pharmacol 52 : 6−17, 2012.

Fenelon M, Quinque E, Arrive E, Catros S, & Fricain J C. Pain−relieving effects of clonazepam and amitriptyline in burning mouth syndrome : a retrospective study. Int J Oral Maxillofac Surg 46 : 1505−1511, 2017.

Fleuret C, Le Toux G, Morvan J, Ferreira F, Chastaing M, Guillet G, & Misery L. Use of selective serotonin reuptake inhibitors in the treatment of burning mouth syndrome. Dermatology 228 : 172−176, 2014.

Freynhagen R, Muth−Selbach U, Lipfert P, Stevens M F, Zacharowski K, Tolle T R, & von Giesen H J. The effect of mirtazapine in patients with chronic pain and concomitant depression. Curr Med Res Opin 22 : 257−264, 2006.

Fukami G, Hashimoto T, Shirayama Y, Hasegawa T, Watanabe H, Fujisaki M, Hashimoto K, & Iyo M. Effects of etizolam and ethyl loflazepate on the P300 event−related potential in healthy subjects. Ann Gen Psychiatry 9 : 37, 2010.

Galli F, Lodi G, Sardella A, & Vegni E. Role of psychological factors in burning mouth syndrome : A systematic review and meta−analysis. Cephalalgia 37 : 265−277, 2017.

Gomez Gomez J M, & Teixido Perramon C. Combined treatment with venlafaxine and tricyclic antidepressants in depressed patients who had partial response to clomipramine or imipramine : initial findings. J Clin Psychiatry 61 : 285−289, 2000.

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 38 : 1−211, 2018.

Jaaskelainen S K. Is burning mouth syndrome a neuropathic pain condition? Pain 159 : 610−613, 2018.

Kato Y, Sato T, Katagiri A, Umezaki Y, Takenoshita M, Yoshikawa T, Sato Y, & Toyofuku A. Milnacipran dose−effect study in patients with burning mouth syndrome. Clin Neuropharmacol 34 : 166−169, 2011.

Kim M J, & Kho H S. Understanding of Burning Mouth Syndrome Based on Psychological Aspects. Chin J Dent Res 21 : 9−19, 2018.

Kremer M, Yalcin I, Goumon Y, Wurtz X, Nexon L, Daniel D, Megat S, Ceredig R A, Ernst C, Turecki G, Chavant V, Theroux J F, Lacaud A, Joganah L E, Lelievre V, Massotte D, Lutz P E, Gilsbach R, Salvat E, & Barrot M. A dual noradrenergic mechanism for the relief of neuropathic allodynia by the antidepressant drugs duloxetine and amitriptyline. J Neurosci 2018.

Lawson K. A Brief Review of the Pharmacology of Amitriptyline and Clinical Outcomes in Treating Fibromyalgia. Biomedicines 5 : 2017.

Maina G, Vitalucci A, Gandolfo S, & Bogetto F. Comparative efficacy of SSRIs and amisulpride in burning mouth syndrome : a single−blind study. J Clin Psychiatry 63 : 38−43, 2002.

Matsuoka H, Chiba I, Sakano Y, Toyofuku A and Abiko Y. Cognitive behavioral therapy for psychosomatic problems in dental settings. BioPsychoSocial Medicine 11 : 18, 2017.

McMillan R, Forssell H, Buchanan J A, Glenny A M, Weldon J C, & Zakrzewska J M. Interventions for treating burning mouth syndrome. Cochrane Database Syst Rev 11 : CD002779, 2016.

Moret C. Combination/augmentation strategies for improving the treatment of depression. Neuropsychiatr Dis Treat 1 : 301−309, 2005.

Pae C U, Marks D M, Shah M, Han C, Ham B J, Patkar A A, & Masand P S. Milnacipran : beyond a role of antidepressant. Clin Neuropharmacol 32 : 355−363, 2009.

PIPC, Psychitry in Primary Care. http : //pipc−jp.com, 2018.

Rojo J E, Ros S, Aguera L, de la Gandara J, & de Pedro J M. Combined antidepressants : clinical experience. Acta Psychiatr Scand Suppl 25−31, 36, 2005.

Vuilleumier P H, Besson M, Desmeules J, Arendt−Nielsen L, & Curatolo M. Evaluation of anti−hyperalgesic and analgesic effects of two benzodiazepines in human experimental pain : a randomized placebo−controlled study. PLoS One 8 : e43896, 2013.

Watanabe Y, Saito H, & Abe K. Tricyclic antidepressants block NMDA receptor−mediated synaptic responses and induction of long−term potentiation in rat hippocampal slices. Neuropharmacology 32 : 479−486, 1993.

Welsch P, Uceyler N, Klose P, Walitt B, & Hauser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. Cochrane Database Syst Rev 2 : CD 010292, 2018.

Xu Y, Bai S J, Lan X H, Qin B, Huang T, & Xie P. Randomized controlled trials of serotonin−norepinephrine reuptake inhibitor in treating major depressive disorder in children and adolescents : a meta−analysis of efficacy and acceptability. Braz J Med Biol Res 49 : 2016.

Durga PAUDEL

Education :

2008–2014 : Bachelor of Dental Surgery (BDS) from Tribhuvan University.

2017 : Joined Health Sciences University of Hokkaido, School of Dentistry as a graduate student.

Professional experience :

2014–2015 : Dental Surgeon at Kathmandu Dental Clinic, Nepal.

2015–Present : Dental surgeon/ Faculty at Kathmandu University Hospital, Dhulikhel, Nepal.