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·临床研究·

长期口服奥美拉唑引起灼口综合征样症状6例临床分析及文献回顾

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【摘要】 目的　分析奥美拉唑引起的灼口综合征样不良反应，为临床合理用药提供参考。**方法**　收集2019年1月至2020年6月于广西医科大学第一附属医院就诊的关于奥美拉唑引起灼口综合征样改变的6例临床病例，并结合相关文献进行回顾性分析。**结果**　在6例患者中，口服奥美拉唑时间最短6个月，最长超过5年，引起的灼口综合征样症状主要为口腔烧灼感，舌部感觉异常，可伴有肢端麻木，患者停服奥美拉唑，给予补充维生素及微量元素治疗，对症治疗1个月至半年后症状基本消失。文献回顾表明其原因可能与奥美拉唑引起外周神经或中枢神经损伤、改变唾液成分及妨碍维生素及微量元素摄入有关。**结论**　奥美拉唑引起灼口综合征样症状原因可能为药物导致的神经损伤、唾液性状改变等，其主要处理方法为停药及对症治疗。

【关键词】 奥美拉唑；　灼口综合征；　不良反应；　感觉异常；　周围神经损伤；　肢端麻木
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Clinical analysis and literature review of 6 cases of burning mouth syndrome-like symptoms caused by the long-term oral administration of omeprazole

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【Abstract】 Objective　To analyze the oral adverse drug reactions induced by omeprazole and provide a reference for rational clinical drug use. **Methods**　From January 2019 to June 2020, the clinical data of patients with burning mouth syndrome caused by omeprazole were collected and analyzed. Additionally, the related literature was reviewed. **Results**　Among the six patients, omeprazole was taken orally for as little as 6 months and as long as more than 5 years. The symptoms of burning mouth syndrome were mainly burning sensation in the mouth and paresthesia on the tongue that might be accompanied by extremity numbness. Vitamin and trace element supplementation was administered. The patient discontinued omeprazole, and symptoms disappeared after symptomatic treatment for 1 month to half a year. Literature review suggests that the reason may be associated with peripheral or central nervous system injury, altered saliva composition, and impaired vitamin and micronutrient intake caused by omeprazole. **Conclusion**　The

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cause of burning mouth syndrome-like symptoms may be related to peripheral nerve injury caused by omeprazole and saliva changes. The main treatment is withdrawal and symptomatic treatment.

【Key words】 omeprazole; burning mouth syndrome; adverse effects; paresthesia; peripheral nerve injuries; acroanesthesia

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灼口综合征(burning mouth syndrome, BMS)是一种以口腔内烧灼样疼痛、口腔黏膜感觉异常为主要临床表现,且不伴有明显临床及病理损害的一组综合征[1]。BMS好发于舌部,女性中较为多见,尤其是围绝经期及绝经后期的中老年女性的发病率更高[2]。BMS相关的发病原因很多,如局部不良刺激、微生物感染、变态反应、唾液成分改变、精神心理、神经系统、内分泌紊乱、维生素和微量元素缺乏等都可引起BMS。奥美拉唑作为质子泵抑制剂,是针对消化道疾病应用广泛且效果显著的抑酸药物[3]。随着奥美拉唑的应用越来越广泛,有关口腔副反应的报道集中在口干及口腔溃疡等[4]。而其引起灼口综合征(burning mouth syndrome, BMS)样症状未见报道,本文旨在分析其引起灼口综合征样症状的情况。现将收治的6例口服奥美拉唑引起BMS样症状患者报告如下。

1　病例资料

收集2019年1月至2020年6月于广西医科大学第一附属医院口腔科就诊的关于长期服用奥美拉唑引起BMS样改变的临床病例。本研究6名患者皆为女性,多为其他科室以"灼口综合征"转入我科,年龄为35~64岁,均有不同程度的口唇及颊部感觉异常,且1例伴有肢端麻木;均未发现口腔黏膜尤其舌部糜烂、溃疡、乳头萎缩、白斑、条纹样改变等异常表现,仅1例有少许潮红。5例患者有长期服用奥美拉唑病史(大于1年),服药1年以上后出现BMS样症状;另1例服药半年后即出现BMS样症状,给药途径均为口服给药(表1)。

表1　奥美拉唑引起灼口综合征样症状患者基本情况

Table 1　Basic information of patients with burning mouth syndrome like symptoms caused by omeprazole

Case	Age(years)	Sex	Past history	Reasons for taking omeprazole	Duration of taking omeprazole
1	39	Female	Abnormal sensation of extremities for 1 year; high postprandial blood sugar, unknown cause	Stomach trouble, unknown cause	More than 3 years
2	59	Female	Denial of a history of trauma, surgery, allergies and other special conditions	Chronic gastritis	5 years
3	54	Female	Denial of a history of trauma, surgery, allergies and other special conditions	Stomach trouble, unknown cause	More than 3 years
4	64	Female	Denial of a history of trauma, surgery, allergies and other special conditions	Chronic gastritis	3 years
5	35	Female	Denial of a history of trauma, surgery, allergies and other special conditions	Reflux esophagitis	6 months
6	59	Female	Denial of a history of trauma, surgery, allergies and other special conditions	Gastritis with bile reflux	More than 5 years

2　结　果

本组6例病例均为服用奥美拉唑后发生BMS样症状,均出现口腔及舌部烧灼样疼痛,1例患者伴有口干,其余患者均不伴口干。5例患者口腔黏膜外观正常,仅1例患者舌部黏膜稍潮红;2例患者口腔黏膜有触痛,疼痛不明显,1例患者右耳后、颊部及口角按压疼痛,其余无触痛。在排除其他刺激因素(过锐牙尖、不良修复体、白色念珠菌感染、残根残冠等)后症状无好转。均给予患者停药处理,其中2例患者服用维生素B1、B12,其余患者告知可自行补充维生素。3例病人停药1个月至半年后自觉口腔烧灼感消失;2例停药3月后自觉明

显好转；1人停药半年后症状好转，但仍有口腔感觉异常（表2）。表明该BMS样改变与奥美拉唑有关，停药后症状不能立即消退，可持续至停药后半年以上。

表2　奥美拉唑引起灼口综合征样症状患者治疗情况

Table 2　Treatment of patients with burning mouth syndrome-like symptoms caused by omeprazole

Case	Symptoms and Chief complaints	Physical examination	Treatment	Treatment effect
1	Dry mouth and burning sensation in the mouth for 1 year	The oral mucosa was normal, with no obvious erosion or ulcer; palpation pain was not obvious	Discontinue Ome; take vitamin B1 and B12	Six months after the withdrawal of the drug, the condition improved, but an abnormal feeling persisted
2	Discomfort due to burning pain in both cheeks for 3 months. No dry mouth	Blunt pain in the right retroauricular region, and buccal and oral corners. No mucosal ulcer was observed	Ome was replaced under the guidance of a gastroenterologist	Improvement after stopping Ome, and BMS symptoms disappeared
3	Tingling Discomfort of tongue for 1 year	No tongue abnormalities were found	Sharpen the cusp of the tooth, pull out the residual root and crown, and discontinue Ome	No improvement after removing some other factors, but improvement after stopping Ome. BMS symptoms disappeared
4	Burning sensation in the tongue and pharynx for 2 years	The mucosa of the tongue was slightly flushed; palpation pain was not obvious	Discontinue Ome; Take vitamin B1 and B12	Improvement after stopping Ome. BMS symptoms disappeared
5	Hot Sensation on the tip of the tongue and oral cavity for 1 month	No problem with the oral mucosa	Sharpen the cusp of the tooth, and discontinue Ome	No improvement after sharpening the cusp, but improvement after stopping Ome
6	Abnormal sensation of the tongue for half a year	The color of the gingiva and buccal mucosa were normal. The tongue was not obviously degenerated and ulcerated	Remove all poor mouth restoration, and stop taking Ome	No improvement after removing all poor mouth restoration, but improvement after the withdrawal of Ome

Ome: Omeprazole; BMS: burning mouth syndrome

3　讨　论

近年来多项研究表明，BMS患者出现的多种口内不适症状可能与其外周神经或中枢神经存在的损伤或异常有关[5]。Puhakka等[6]通过定量感官实验证实了部分BMS患者存在疼痛部位局部的外周神经纤维病变，BMS患者舌黏膜组织病理检查发现上皮内神经纤维明显减少。Grémeau-Richard等[7]发现部分BMS患者的中枢神经系统存在病理学方面的变化，其面部神经和三叉神经感觉功能之间的异常相互作用，鼓索神经的传入纤维Aδ纤维功能减退，味觉阈值降低，而菌状乳头主要由鼓索神经纤维及舌神经支配[8]。根据这一理论，Kamala等[9]发现部分灼口综合征患者由于舌前部有较多菌状乳头，因而会出现烧灼感。

奥美拉唑引起BMS样症状的机制尚不明确。奥美拉唑是一种弱碱基的前体药物，其在体外活性较小，激活有pH依赖性，在中性条件下稳定，弱酸条件下较稳定，强酸条件下有强作用。因此，其在胃壁细胞内小管这一高酸性环境中才被浓缩转化为活性物质。一旦奥美拉唑在细胞内被激活，它就与半胱氨酸残基结合形成二硫键暴露在细胞膜上并抑制活性H^+/K^+-ATP酶[10]。奥美拉唑常见的不良反应为恶心、呕吐、腹痛、腹泻、便秘、血清转氨酶和胆红素升高、神经系统损伤等[10]，但未见引起BMS样口腔感觉异常的报道。Forgerini等[11]表明口服奥美拉唑可出现指端麻木，引起周围神经病变，其机理可能与其在亚细胞水平上的极细微的生化变化有关。本研究也发现有1例患者伴有肢端麻木。Suzuki等[12]研究表明质子泵抑制剂亦可引起中枢神经副作用，显著降低舌前部（鼓索神经区）和舌后部（舌咽部）味觉阈值。而如前述，味觉阈值降低是导致灼口综合征的重要原因。因此，奥美拉唑作为质子泵抑制剂，引起的BMS样症状可能为奥美拉唑引起周围神经损伤导致的，其对中枢神经的损伤也有一定的协同作用。

此外，奥美拉唑也可能在抑制胃酸分泌的同时导致唾液分泌成分的改变，引起口腔和肠道微生物群的改变[13]。研究表明奥美拉唑给药后唾液

pH显著增加[14]。于习习及Acharya等[15-16]均发现唾液成分的改变可导致口干及口腔辣痛感。Proctor等[17]也发现唾液成分改变导致口腔神经病变和神经传导障碍,引起BMS。另一方面,可能是奥美拉唑妨碍某些维生素及微量元素的吸收,可导致铁缺乏症、维生素B12缺乏症[18]。维生素B12为细胞生长分裂及维持神经组织髓鞘完整所必需的物质,可维持黏膜上皮细胞的正常代谢和功能。锌、铜、铁、镁等的吸收与代谢互有影响,出现异常会产生多种代谢紊乱[19]。人体中这些维生素及微量元素的缺乏可导致BMS的发生。

综上所述,奥美拉唑所致的BMS症状主要有舌及口唇黏膜麻木,可伴有肢端麻木。对于奥美拉唑所致的BMS,应停药,补充维生素B12及微量元素;告知患者停药后症状完全消退可能需要半年;提醒患者短期内不要重新服用该药;对中老年女性这类BMS易感人群的胃病治疗,建议改用其他抗酸药。

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参考文献

[1] Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition[J]. Cephalalgia, 2018, 38(1): 1-211. doi: 10.1177/0333102417738202.

[2] Bender SD. Burning mouth syndrome[J]. Dent Clin North Am, 2018, 62(4): 585-596. doi: 10.1016/j.cden.2018.05.006.

[3] Qi Q, Wang RG, Liu L, et al. Comparative effectiveness and tolerability of esomeprazole and omeprazole in gastroesophageal reflux disease: a systematic review and meta-analysis[J]. Int J Clin Pharmacol Ther, 2015, 53(10): 803-810. doi: 10.5414/CP202396.

[4] Cheong PK, Ford AC, Cheung C, et al. Low-dose imipramine for refractory functional dyspepsia: a randomised, double-blind, placebo-controlled trial[J]. Lancet Gastroenterol Hepatol, 2018, 3(12): 837-844. doi: 10.1016/S2468-1253(18)30303-0.

[5] Jääskeläinen SK. Is burning mouth syndrome a neuropathic pain condition?[J]. Pain, 2018, 159(3): 610 - 613. doi: 10.1097/j.pain.0000000000001090.

[6] Puhakka A, Forssell H, Soinila S, et al. Peripheral nervous system involvement in primary burning mouth syndrome--results of a pilot study[J]. Oral Dis, 2016, 22(4): 338-344. doi: 10.1111/odi.12454.

[7] Grémeau-Richard C, Dubray C, Aublet-Cuvelier B, et al. Effect of lingual nerve block on burning mouth syndrome (stomatodynia): a randomized crossover trial[J]. Pain, 2010, 149(1): 27 - 32. doi: 10.1016/j.pain.2009.11.016.

[8] Witt M. Anatomy and development of the human taste system[J]. Handb Clin Neurol, 2019, 164: 147-171. doi: 10.1016/B978-0-444-63855-7.00010-1.

[9] Kamala KA, Sankethguddad S, Sujith SG, et al. Burning mouth syndrome[J]. Indian J Palliat Care, 2016, 22(1): 74 - 79. doi: 10.4103/0973-1075.173942.

[10] Daure E, Ross L, Webster CR. Gastroduodenal ulceration in small animals: part 2. proton pump inhibitors and histamine-2 receptor antagonists[J]. J Am Anim Hosp Assoc, 2017, 53(1): 11-23. doi: 10.5326/JAAHA-MS-6634.

[11] Forgerini M, Mieli S, Mastroianni PC. Safety assessment of omeprazole use: a review[J]. Sao Paulo Med J, 2018, 136(6): 557-570. doi: 10.1590/1516-3180.2018.0019220318.

[12] Suzuki M, Yokota M, Matsumoto T, et al. Proton pump inhibitor ameliorates taste disturbance among patients with laryngopharyngeal reflux: a randomized controlled study[J]. Tohoku J Exp Med, 2019, 247(1): 19-25. doi: 10.1620/tjem.247.19.

[13] Mishiro T, Oka K, Kuroki Y, et al. Oral microbiome alterations of healthy volunteers with proton pump inhibitor[J]. J Gastroenterol Hepatol, 2018, 33(5): 1059-1066. doi: 10.1111/jgh.14040.

[14] Wang YJ, Lang XQ, Wu D, et al. Salivary pepsin as an intrinsic marker for diagnosis of sub-types of gastroesophageal reflux disease and gastroesophageal reflux disease-related disorders[J]. J Neurogastroenterol Motil, 2020, 26(1): 74 - 84. doi: 10.5056/jnm19032.

[15] 于习习, 吕健, 王彩霞, 等. 维生素B1与B12肌肉注射对灼口综合征患者疼痛、唾液及味觉的影响[J]. 口腔疾病防治, 2018, 26(4): 240-244. doi: 10.12016/j.issn.2096-1456.2018.04.008.
Yu XX, Lu J, Wang CX, et al. The effects of intramuscular injections of vitamin B1 and B12 on pain, salivary components and taste in patients with burning mouth syndrome[J]. J Prev Treat Stomatol Dis, 2018, 26(4): 240-244. doi: 10.12016/j.issn.2096-1456.2018.04.008.

[16] Acharya S, Hägglin C, Jontell M, et al. Saliva on the oral mucosa and whole saliva in women diagnosed with burning mouth syndrome[J]. Oral Dis, 2018, 24(8): 1468-1476. doi: 10.1111/odi.12918.

[17] Proctor GB. The physiology of salivary secretion[J]. Periodontol 2000, 2016, 70(1): 11-25. doi: 10.1111/prd.12116.

[18] Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors[J]. Expert Rev Clin Pharmacol, 2013, 6(4): 443 - 451. doi:10.1586/17512433.2013.811206.

[19] 于习习, 王彩霞, 王万春. 原发性灼口综合征相关研究进展[J]. 口腔疾病防治, 2018, 26(12): 810-816. doi: 10.12016/j.issn.2096-1456.2018.12.011.
Yu XX, Wang CX, Wang WC, et al. Research progress on primary burning mouth syndrome [J]. J Prev Treat Stomatol Dis, 2018, 26(12): 810-816. doi: 10.12016/j.issn.2096-1456.2018.12.011

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