Drug-induced burning mouth syndrome: a new etiological diagnosis

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Abstract

Burning mouth syndrome (BMS) is defined as a burning sensation of the oral mucosa, in the absence of specific oral lesions. The underlying etiology remains unclear. Peripheral alterations may be related to the density or reactive capacity of the oral mucosal membrane receptors - these being largely influenced by BMS-related risk factors such as stress, anxiety, the female gender, climacterium and advanced age. The present study compiles the cases of BMS induced by drugs reported in the literature, and attempts to draw a series of conclusions. A search was conducted in the PubMed® database using the following key words: burning mouth syndrome, drug-induced, antihypertensive and chemically-induced. The search was carried out in April 2007. The literature yielded clinical cases in which oral burning sensation is described after the administration of drugs belonging to different therapeutic groups: antiretrovirals, antiseizure drugs, hormones and particularly antihypertensive medication. Curiously, among the different types of antihypertensive drugs, BMS was only associated with those compounds that act upon the angiotensin-renin system.

Key words: *Burning mouth syndrome, drug-induced, antihypertensive drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists.*

The etiology underlying burning mouth syndrome (BMS) remains uncertain. The disorder is characterized by a burning or itching sensation preferentially located at the tip and sides of the tongue, lips and anterior palate, in the absence of evidence of oral mucosal pathology (1), and sometimes associated with taste alterations and dry mouth (2,3). The manifestations of BMS are usually bilateral, but in some cases may prove unilateral.

The syndrome is more common in women than in men - the peak prevalence corresponding to females in the fourth to sixth decades of life (3,4).

The diagnosis of BMS requires careful evaluation of the symptoms, with due consideration of a series of inclusion criteria (5): (a) burning sensation located in some area of the oral mucosa; (b) persistence of the manifestations for at least 4-6 months; (c) continuous burning sensation throughout the day, or with increased intensity towards the afternoon-evening; (d) infrequent associated sleep disturbances; and (e) symptoms relief upon eating or drinking.

Cerchiari (6) classified BMS according to the associated risk factors: idiopathic, psychogenic, local and systemic. Among the psychogenic risk factors, mention should be made of psychopathological processes such as anxiety,

depression and certain phobias. The local factors in turn comprise infectious processes, allergic reactions and irritative phenomena, while the systemic etiological factors include alterations in salivary secretion, endocrine disorders, neurological alterations, nutritional factors, and drug substances.

Antihypertensive agents are the drugs most often associated with the appearance of symptoms compatible with BMS. Likewise, among the different types of antihypertensive drugs, those related to the appearance of burning mouth sensation are compounds that act upon the angiotensin-renin system.

Among the drugs reported to induce manifestations similar to those of BMS, mention should be made of efavirenz (7), an antiretroviral agent that inhibits reverse transcriptase of the human immunodeficiency virus (HIV); the antiseizure drug clonazepam(8), which paradoxically is the compound offering the best results in the management of BMS, with a remission rate of up to 40% (9-11); hormone replacement therapy (HRT)(12); the antidepressants fluoxetine, sertraline and venlafaxine(13); and a broad range of antihypertensive agents, including captopril, enalapril, lisinopril, eprosartan and candesartan (14-19).

Of the global cases of drug-induced BMS, 33% were seen to be dose-dependent phenomena, since the burning sensation appeared on elevating the drug dose in search of increased therapeutic efficacy. No relationship was found between the duration of treatment and appearance of the symptoms.

Some cases have been associated with risk factors such as depression, anxiety or menopause (20-22). Moreover, in all cases corresponding to females, the latter were of postmenopausal age.

Of the 9 documented cases of BMS induced by antihypertensive drugs, a little over half were women. Bergdahl et al. (3) reported that for every male diagnosis of BMS, 3.44 women are diagnosed with the disorder. In the present review, the female predominance in BMS was 1.25/1. The three documented cases associated with captopril corresponded to women, while the three cases associated with enalapril corresponded to males.

A number of authors have found antihypertensive agents to be the drugs most often associated with the appearance of symptoms compatible with BMS (23-25). This is supported by the scientific literature searches of drug-induced cases of BMS (Table 1).

At present, arterial hypertension can be treated with a broad range of drugs belonging to 5 therapeutic categories or groups: diuretics, beta-adrenergic receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers or antagonists (ARBs or ARAII drugs)(26).

Curiously, the only types of antihypertensive drugs associated with BMS-compatible symptoms are those compounds that act upon the angiotensin-renin system, i.e., ACEIs (captopril, enalapril and lisinopril) and ARAII drugs (eprosartan and candesartan)(27,28).

The renin-angiotensin system plays a key role in the regulation of blood pressure. It consists of a cascade of enzyme reactions that lead to the formation of angiotensin II (Figure 1). The first reaction is catalyzed by renin, and consists of the transformation of angiotensinogen into angiotensin. This is followed by the angiotensin-converting enzyme (ACE)-mediated transformation of angiotensin I into angiotensin II, which is the biologically active molecule (29,30).

Table 1. Description of cases of burning mouth syndrome induced by drugs.

AUTHOR	DRUG	ACTIVITY	SEX	AGE	POSOLOGY	TIME [1]
Borras-Blasco et al (7)	Efavirenz	Antiretroviral	F	42	600 mg/24h	2 weeks
Culhane et al (8)	Clonazepam	Anxiolytic	F	52	0.5 mg/12h	4 weeks
Levenson (13)	Fluoxetine	Antidepressant	F	56	30 mg/24h	2 weeks
Levenson (13)	Sertraline	Antidepressant	F	56	100 mg/24h	not stated
Levenson (13)	Venlafaxine	Antidepressant	F	56	not stated	not stated
Triantos et al (14)	Enalapril	Antihypertensive	M	50	20 mg/24h	6 months
Brown et al (17)	Enalapril	Antihypertensive	M	72	10 mg/12h	1 year
Vlasses et al (19)	Enalapril	Antihypertensive	M	54	20 mg/12h	7 days
Vlasses et al (19)	Captopril	Antihypertensive	F	53	25 mg/8h	6 days
Vlasses et al (19)	Captopril	Antihypertensive	F	64	50 mg/8h	9 weeks
Brown et al (17)	Captopril	Antihypertensive	F	54	not stated	7 years
Savino et al (18)	Lisinopril	Antihypertensive	F	74	10 mg/24h	2 months
Chen et al (15)	Candesartan	Antihypertensive	M	46	4 mg/24h	6 months
Castells et al (16)	Eprosartan	Antihypertensive	F	48	600 mg/24h	3 weeks

[1] Time to appearance of burning mouth syndrome after start of treatment

The ACEIs act upon the enzymatic cascade of the renin-angiotensin system, inhibiting ACE and thus preventing the transformation of angiotensin I into angiotensin II. In turn, the ARAII drugs act upon a later step in the cascade, blocking angiotensin II receptor activation. These drugs, which show highly varied chemical structures, ultimately prevent the formation and interaction of angiotensin II with its receptors, thus blocking the activity of the former (Figure 1).

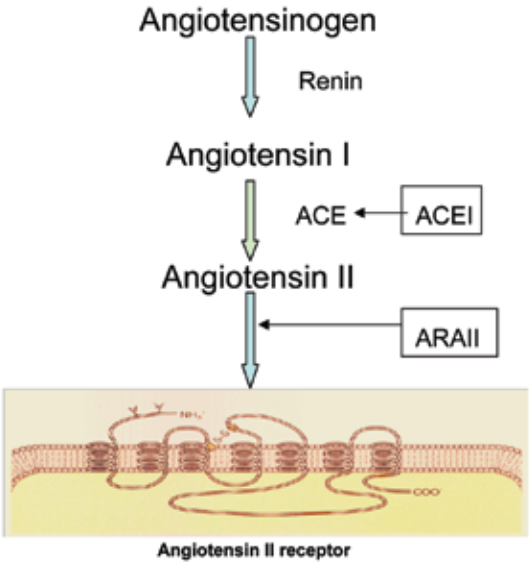

Fig. 1. Mechanism of action of the antihypertensive drugs that act upon the renin-angiotensin system.

Angiotensin II exerts most of its actions by interacting with its receptors located in different organs such as the kidneys, heart, central and peripheral nervous system, and adrenal glands (31,32). Basically, angiotensin II maintains blood pressure via two mechanisms: at vascular level it induces vasoconstriction, and at renal level it inhibits the excretion of water and sodium. These actions directly and indirectly affect cardiovascular and renal homeostasis, participating in the development and maintenance of processes such as arterial hypertension, atherosclerosis, heart failure, myocardial infarction, stroke, renal failure and diabetic nephropathy, among others (33,34).

Different disorders with apparently similar symptoms were grouped from the start under the term BMS. At present, three types of BMS are distinguished (35). Type 1 is characterized by pain that increases during the day, and which may be related to neuropathic disorders. Type 2 involves continuous and stable pain during the day, and is associated with psychiatric alterations. Finally, type 3 is characterized by intermittent pain in unusual locations such as the floor of the mouth, and is associated with the presence of allergens such as preservatives and additives.

Considering that antihypertensive drugs which act upon the renin-angiotensin system have been associated with BMS-like symptoms, and in view of the heterogeneity of the described cases of BMS, the underlying etiology in some situations may involve an anomaly of the renin-angiotensin system that blocks angiotensin II activity and causes burning sensation of the oral mucosa. It would be interesting to search for markers of this enzymatic anomaly in order to determine its prevalence and relationship to the clinical manifestation of BMS.

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