Burning mouth syndrome (BMS): double blind controlled study of alpha-lipoic acid (thioctic acid) therapy

F. Femiano[1]
C. Scully[2]

[1]*Stomatology Clinic II, University of Medicine and Surgery, Napoli, Italy, and*
[2]*Eastman Dental Institute, University College London, London, UK*

Abstract

Background: Burning mouth syndrome (BMS) has features of a neuropathy and could be related to the production of the toxic free radicals that are released in stress situations. Alpha-lipoic acid is an antioxidant able to increase the levels of intracellular glutathione and eliminate free radicals. This study aimed to examine the effectiveness of alpha-lipoic acid in the therapy of BMS.

Method: This was a double blind, controlled study conducted for two months on 60 patients with constant BMS. Comparing alpha-lipoic acid (test) with cellulose starch (placebo), there was no laboratory evidence of deficiencies in iron, vitamins or thyroid function and no hyperglycaemia.

Results and Conclusion: Following treatment with alpha-lipoic acid, there was a significant symptomatic improvement, compared with placebo, with the majority showing at least some improvement after 2 months, thus supporting the hypothesis that burning mouth syndrome is a neuropathy. This improvement was maintained in over 70% of patients at the 1 year follow-up.

Key words: BMS; lipoic acid; neuropathy; oral dysaesthesia

J Oral Pathol Med 2002: **31:** 267–9

The term 'burning mouth syndrome' (BMS) refers to a chronic oral pain, diagnosed in the absence of any visible mucosal abnormality, and where psychogenic factors are a possible cause. BMS pain is mainly described as a feeling that the mouth has been burnt by hot liquid. In most cases, the discomfort intensifies during the course of the day (1, 2). Typically, the tongue is affected, but the anterior palate and lips are also frequently involved (3, 4).

BMS occurs largely, but not exclusively, amongst postmenopausal women. Many cases appear related to psychogenic factors (5–8), although recently the possibility of a neuropathic aetiology was muted, as the pain was reduced by local anaesthesia (9), and alpha-lipoic acid, a free radical scavenger, appeared to reduce the discomfort of BMS in preliminary studies (10).

Correspondence to:
Dr Femiano Felice
via Francesco Girardi 2, S.Antimo (NA), 80029, Italy
e-mail: femiano@libero.it

Accepted for publication May 14, 2001

J Oral Pathol Med . ISSN 0904-2512

Table 1. Scoring of BMS

Change in symptomatology	Scored as
Worsening	−
Unchanged	+ −
Slight improvement	+
Decided improvement	+ +
Resolution	+ + +

We were therefore interested in evaluating the efficacy of alpha-lipoic acid in BMS through a double blind, controlled study.

Patients and methods

A group of 96 patients, diagnosed with BMS from a history of constant burning discomfort in the anterior tongue, lower lip or hard palate, for more than two months, with no relevant drug or medical history, were examined for evidence of clinical oral mucosal lesions and alterations in laboratory parameters (whole blood folate, serum vitamin B12, serum ferritin, serum glucose, thyroid hormone levels) that could be responsible for the BMS. A final study subgroup of 60 subjects with BMS (42 females; ages 22–68 years; median 45 years) was identified with no clinical or laboratory evidence of disease.

The study used two therapeutic protocols, divided at random for two groups of patients, using lipoic acid as test, and cellulose starch as control, where neither the patient nor doctor could distinguish the substance used.

The therapeutic protocols comprised a 2-month trial of alpha-lipoic acid, in 200 mg oral pills, three times a day (Test) or cellulose starch, in similar pills, 100 mg/day, three times a day (Control).

The patients were clinically assessed every 15 days, and symptomatology was recorded as detailed in Table 1, based on a visual analogue scale. Patients that reported any amelioration within 4 months (12 of Control group and 29 of Test group) were given further therapy for 1 month, with a protocol identical to that used previously.

The study was concluded with a re-evaluation of the results 1 year after commencement of the trial.

Table 3. Results at 1 year follow-up for changes in burning symptomatology in all subjects who showed an improvement at 2 months, as shown in Table 2, using alpha lipoic acid (test) or placebo control (starch)

Study groups	No change *n* (%)	Slight deterioration *n* (%)	Significant deterioration *n* (%)
Control $n = 12$	0	2 (17)*	10 (83)*
Test $n = 29$	21 (73)*	3 (10)*	5 (17)*

*Test compared with control, $P < 0.0001$

Statistical analysis

The results were analyzed by chi-squared test.

Results

There was a statistically significant symptomatic improvement with alpha-lipoic acid (97%) used over 2 months, compared with placebo (40%) (Table 2). Indeed, 87% of patients treated with alpha-lipoic acid showed resolution or a decided improvement in symptoms, compared with zero patients taking placebo. None of the patients had worsening BMS whilst on alpha-lipoic acid, yet symptoms increased in 20% of patients taking placebo. Furthermore, the significant symptomatic improvements in BMS treated with alpha-lipoic acid were seen without notable adverse effects.

Follow-up at 12 months showed that any improvement achieved with alpha-lipoic acid was maintained completely in 73%, whereas all controls who had improved during the course of the study had deteriorated to some extent in the interim (Table 3).

Discussion

The diagnosis of BMS is usually made after symptoms are reported over more than 6 months, although in our experience, most patients with symptoms lasting 2 months, as in this study, will have genuine

Table 2. Changes in burning symptomatology using alpha lipoic acid (test) or placebo control (starch) over 2 months

Study groups $n = 30$	Worsening *n* (%)	Unchanged *n* (%)	Slight improvement *n* (%)	Decided improvement *n* (%)	Resolution *n* (%)	Any improvement *n* (%)
Control	6 (20)*	12 (40)*	12 (40)*	0*	0*	12 (40)*
Test	0*	1 (3)*	3 (10)*	22 (74)*	4 (13)*	29 (97)*

*Test compared with control, $P < 0.0001$

BMS. The results of the present study indicate that alpha-lipoic acid is useful in BMS and suggest that it is possible that BMS may be a neuropathy related to free radical production.

Alpha-lipoic acid (thioctic acid) is a natural antioxidant which has been available for years in Europe and has been used to treat radiation sickness, diabetic neuropathy and has also been investigated as a possible HIV-inhibitor (11, 12). Alpha-lipoic acid is a unique free radical protector as it is both fat- and water-soluble and thus has excellent bioavailability. Once it enters the cell, alpha-lipoic acid is broken down into dihydrophilic acid, an even more potent free radical neutralizer (13, 14). Alpha-lipoic acid also helps to conserve other antioxidants, such as vitamin E and C (15), and is able to chelate heavy metals (16).

Alpha-lipoic acid is a sulphur-containing substance that is readily converted to and from its reduced form, dihydrolipoic acid. It acts as a coenzyme in the Krebs cycle; specifically in the decarboxylation of pyruvate and some other alpha-keto acids (17). Alpha-lipoic acid may also be hepatoprotective (14, 16).

Alpha-lipoic acid also elevates cellular levels of glutathione (GSH): low levels of GSH may cause oxidative stress, inflammation and nerve damage, leading to peripheral neuropathy (17–19). In animal studies, significant improvements in nerve conduction velocity have been observed in response to supplementation with alpha-lipoic acid (14).

It is therefore possible that BMS may be a neuropathy related to free radical production and low levels of intracellular glutathione and that alpha-lipoic acid may be beneficial in at least some of the patients with this complaint.

References

1. Wardrop RW, Hailes J, Burger H, et al. Oral discomfort at menopause. *Oral Surg* 1989; **67**: 535–40.
2. Hakeberg M, Berggren U, Hagglin C, Ahlqwist M. Reported burning mouth symptoms among middle-aged and elderly women. *Eur J Oral Sci* 1997; **105**: 539–43.
3. Savage NW. Burning mouth syndrome: patient management. *Aust Dent J* 1996; **41**: 363–6.
4. Tammiala-Salonen T, Forssell H. Trazodone in burning mouth pain: a placebo-controlled, double-blind study. *J Orofac Pain* 1999; **13**: 83–8.
5. Marbach JJ. Medically unexplained chronic orofacial pain. Temporomandibular pain and dysfunction syndrome, orofacial phantom pain, burning mouth syndrome, and trigeminal neuralgia. *Med Clin North Am* 1999; **83**: 691–710.
6. Browning S, Hislop S, Scully C, et al. The association between burning mouth syndrome and psychosocial disorders. *Oral Surg* 1987; **64**: 171–4.
7. Murray M, Pizzorno J. Encyclopedia of Natural Medicine, 2nd edn. Rocklin: Prima Publishing, 1998: 768–84.
8. Lauritano D, Spadari F, Formaglio F, Zambellini Artini M, Salvato A. Etiopathogenic, clinical-diagnostic and therapeutic aspects of the burning mouth syndrome. Research and treatment protocols in a patient group. *Minerva Stomatol* 1998; **47**: 239–51.
9. Formaker BK, Mott AE, Frank ME. The effects of topical anesthesia on oral burning in burning mouth syndrome. *Ann N Y Acad Sci* 1998; **30**: 776–80.
10. Femiano F, Gombos F, Scully C, De Busciolano M, Luca P. Burning Mouth syndrome (BMS): controlled open trial of the efficacy of alpha-lipoic acid (thioctic acid) on symptomatology. *Oral Dis* 2000; **6**: 274–7.
11. Jacob S, Streeper RS, Fogt DL, et al. The antioxidant alpha-lipoic acid enhances insulin-stimulated glucose metabolism in insulin-resistant rat skeletal muscle. *Diabetes* 1996, **45**: 1024–9 and 0012–1797.
12. Grieb G. Alpha-lipoic acid inhibits HIV replication. *Med Monatsschr Pharm* 1992; **15**: 243–4.
13. Merin JP, Matsuyama M, Kira T, Baba M, Okamoto T. Alpha-lipoic acid blocks HIV-1 LTR-dependent expression of hygromycin resistance in THP-1 stable transformants. *FEBS-Lett* 1996; **23**: 394: 9–13 and 0014–5793.
14. Ruhnau KJ, Meissner HP, Finn JR, et al. Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy. *Diabet Med* 1999; **16**: 1040–3.
15. Packer L, Tritschler HJ, Wessel K. Neuroprotection by the metabolic antioxidant alpha-lipoic acid. *Free Radic Biol Med* 1997; **22**: 359–78.
16. Ziegler D, Gries FA. Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. *Diabetes* 1997; **46**: S62–6.
17. Arivazhagan P, Panneerselvam C. Effect of DL-alpha-lipoic acid on neural antioxidants in aged rats. *Pharmacol Res* 2000; **42**: 219–22.
18. Kelly GS. Nutritional and botanical interventions to assist with the adaptation to stress. *Altern Med Rev* 1999; **4**: 249–65.
19. Tirosh O, Sen CK, Roy S, Kobayashi MS, Packer L. Neuroprotective effects of alpha-lipoic acid and its positively charged amide analogue. *Free Radic Biol Med* 1999; **26**: 1418–26.