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ORIGINAL ARTICLE

α-Lipoic acid treatment of 31 patients with sore, burning mouth

JC Steele, AJ Bruce, LA Drage, RS Rogers, III

Department of Dermatology, Mayo Clinic, Rochester, MN, USA

OBJECTIVE: To review a series of patients with sore, burning mouth treated with α-lipoic acid between 2000 and May 2006 and subjectively evaluate improvement in symptoms.

DESIGN: Retrospective review of medical records of 195 consecutive patients who sought treatment for sore, burning mouth. Treatment of 47 patients was a prescription/recommendation for α-lipoic acid. Of these patients, 35 were available for follow-up.

SETTING: Tertiary care academic medical center.

SUBJECTS: Ambulatory patients given prescription/recommendation for α-lipoic acid 600 mg per day, in divided doses.

MAIN OUTCOME MEASURE: Reported improvement in symptoms documented in medical records and at follow-up (visits or telephone interviews).

RESULTS: Thirty-one of the 35 patients (66% of all 47) actually took α-lipoic acid as recommended. No patient reported a complete alleviation of symptoms. Six (19%) of these 31 patients felt mostly better, five (16%) felt somewhat better, and 14 (45%) reported no difference. Two patients (7%) reported a worsening of symptoms and four (13%) did not know whether there had been improvement.

CONCLUSION: Eleven of 31 patients (35%) reported benefit from taking α-lipoic acid. Because we examined only a small number of patients and relied on a subjective outcome assessment, further larger studies using a prospective, randomized, controlled, and double-blind structure are warranted.

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Keywords: α-lipoic acid; burning mouth; retrospective study

Introduction

The varied medical nomenclature used to describe a burning sensation in the oral mucosa includes burning mouth syndrome (BMS), glossodynia, stomatodynia, glossopyrosis, stomatopyrosis, and oral dysesthesia. Whether the condition is a syndrome, as in BMS, or a symptom of some other process is debatable. In this paper, we report our review of the treatment and outcomes of patients who presented with a sore, burning mouth but had no abnormality of the oral mucosa identified on clinical examination of the oral cavity (e.g., hematuric deficiencies, diabetes mellitus, candidiasis, xerostomia, or denture use).

Various potentiating or precipitating factors may initiate the burning sensation experienced by patients (Drage and Rogers, 2003; Drage *et al*, 2006). A previous report from our institution suggested good success with a multidisciplinary approach to the management of sore, burning mouth, with 72% of patients who had follow-up reporting improvement in symptoms (Drage and Rogers, 1999). A recent paper by Sardella *et al* (2006) gave a more pessimistic outlook in terms of spontaneous resolution of BMS symptoms (3.7%), with only 28.3% of patients having moderate improvement after treatment.

α-Lipoic acid (ALA; thioctic acid) is a readily available over-the-counter metabolic antioxidant suggested for alleviation of the troublesome symptoms of BMS, either alone or in conjunction with psychotherapy. According with a Cochrane Database meta- analysis conducted by Zakrzewska *et al* (2005), three clinical trials assessing the effectiveness of ALA demonstrated some benefit (i.e., improvement in BMS symptoms).

α-Lipoic acid (1,2-dithiolane-3-pentanoic acid) is a natural mitochondrial co-enzyme and hepatic protectant that is important in certain reactions in the tricarboxylic acid cycle (Krebs cycle) and in glycolysis. Other antioxidants, such as vitamins C and E, are regenerated through the reactions in which ALA is involved. ALA also increases intracellular glutathione levels. It is both water- and fat-soluble, which gives it a greater site of action to neutralise free radicals compared with other antioxidants (Tirosh *et al*, 1999). ALA has been used with various degrees of success in the treatment of patients with cardiac autonomic neuropathy (Ziegler *et al*, 1997), dementia, diabetic neuropathy, hyperglycemia, lactic acidosis, liver disease, and mushroom poisoning (AltMedDex® System).

Correspondence: AJ Bruce, Department of Dermatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. E-mail: bruce.alison@mayo.edu
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Patients and methods

Approval for this retrospective study was obtained from the Mayo Clinic Institutional Review Board. We examined data from the medical records of 195 consecutive patients seen for sore, burning mouths in the Department of Dermatology by two of us (R.S.R. and A.J.B.) at Mayo Clinic, Rochester, between 2000 and May 2006. A larger study on the entire group of patients is the subject of another paper in preparation. Eighteen patients with a mucosal diagnosis were eliminated from analysis. These diagnoses included geographic tongue (erythema migrans, benign migratory glossitis) and oral lichen planus. Of the 177 other patients with burning mouth, 47 were given a prescription for or a recommendation to purchase over-the-counter ALA. Their electronic medical records were reviewed and information from these consultations (e.g., clinical and laboratory findings) were summarized. Follow-up data were obtained by reviewing subsequent consultations or by conducting a structured telephone interview with the patient. (All telephone calls were made by J.C.S.)

Results

Of the 47 patients (35 women and 12 men) who received a prescription or a recommendation for ALA, 35 (74%; 25 women and 10 men) were followed up by telephone interview. Of the rest, two patients refused to participate, one did not speak English, and nine were lost to follow-up.

All 35 patients purchased ALA after it was prescribed or recommended. However, four of these patients decided not to take it, leaving a study cohort of 31 patients [22 women (71%), and nine men (29%)]. The mean age at which the symptoms commenced was 60.6 years (range, 32–84 years) for 30 of the 31 available patients.

The chief complaint for 27 patients (87%) was a burning sensation in the mouth. Fifteen patients (48%) had a subjective feeling of a dry mouth (xerostomia). Of four patients who complained of a bad taste in the mouth, one also complained of a decreased sense of taste.

With regard to comorbid conditions, eight patients had controlled hypertension, two had diabetes mellitus, seven had a history of hypothyroidism but were now euthyroid with replacement therapy, 11 carried a diagnosis of depression, five had previously diagnosed anxiety and nine had been treated for gastroesophageal reflux disease. Three of the 31 patients were smokers, five were former smokers, and 23 had never smoked.

The tongue was the most common site of the burning sensation, with 24 patients (77%) thus affected. The next most common sites were the palate (13 patients) and the lips (nine patients). Other sites included the gingivae, the throat and the buccal mucosa (two patients each) and the floor of the mouth (one patient).

No mucosal abnormality (e.g., inflammation, erythema, erosion, ulceration, or hyperkeratosis) was documented on any physical examination report for these patients. However, 17 patients (55%) had oral mucosal dryness and six patients wore dentures.

Oral dryness was corrected for the patients affected by it with the use of sialogogues or salivary replacements. Dietary irritants were identified and eliminated, and underlying vitamin deficiencies were corrected. Any associated candidiasis was treated before initiation of ALA treatment.

The dose of ALA recommended to patients was 600 mg per day in divided doses of either 200 mg three times daily or 300 mg twice daily. This degree of ALA therapy was in keeping with all of the published reports on ALA in the medical literature to date. Of the 31 patients who started taking ALA, nine are still doing so.

Data were available for 29 of the 31 patients on the duration of their course of ALA. The mean course of treatment was 26.6 weeks (range, 4–80 weeks). Although all patients were encouraged to take ALA 600 mg per day in divided doses, the follow-up interview revealed that some patients took different combinations of doses (some by recommendation of a physician after a 12-week standard course of therapy).

Twenty-five patients reported taking a combination of doses ranging from 100 mg daily (minimum) to 600 mg daily (maximum). Six patients could not recall what dose they had taken. According to these results, 19 patients took the recommended dose of 600 mg per day in divided doses (Figure 1).

The patients who took the medication were contacted by telephone and asked to rate the effect of ALA on their burning mouth symptoms (Table 1). Four patients reported side effects after taking ALA. These included heartburn in two patients and gastritis and nausea in one patient each (Drage and Rogers, 2003). Typically reported adverse effects of ALA are muscle cramps, paresthesia, and initial worsening of neuropathy symptoms, platelet disorders, purpura, shortness of breath, tension headache, urticaria, and eczema (AltMedDex® System). Nausea and vomiting usually occur only with

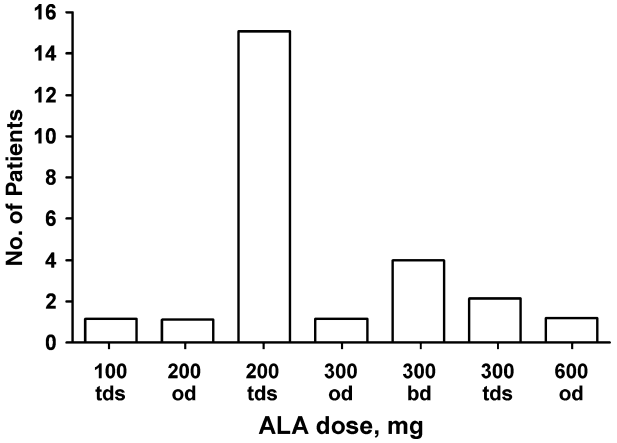

Figure 1 Of the 31 patients who took α-lipoic acid for sore, burning mouths, 25 reported taking doses ranging from 200 to 900 mg daily. The most common dose was 200 mg three times daily (bd, twice daily; od, once daily; tds, three times daily)

Table 1 Effects of α-lipoic acid on symptoms of sore, burning mouth[a]

Response	*n*	*%*[b]
Worse	2	6
Same or no difference	14	45
Somewhat better	5	16
Mostly better	6	19
Completely better	0	0
Do not know	4	13

[a]Responses of 31 patients to the follow-up question: 'Has α-lipoic acid made your symptoms ____?'
[b]$n = 31$. Percentages total < 100% because of rounding.

doses higher than the 600 mg per day that had been recommended to our patients.

Discussion

In a meta-analysis undertaken for the Cochrane Database of Systematic Reviews (Zakrzewska *et al*, 2005), ALA was only one of three interventions that produced a reduction in BMS symptoms; the other treatments were anticonvulsants and cognitive behavioral therapy. Two of these studies were open-label and one study was double-blind. In the initial report of the open-label trial published in 2000 by Femiano *et al* (2000), 76% of patients showed some improvement after 30 days. In a subsequent double-blind, controlled study by the same investigators (Femiano and Scully, 2002), 97% showed some improvement by 2 months. In a later report of an open-label trial (Femiano, 2002), the same group of researchers compared ALA with other treatments and found that 90% of those treated with ALA had some improvement. Zakrzewska *et al* (2005) suggested caution in interpreting the outcome assessment of the two open-label trials because of their subjective nature.

Aside from those studies identified in the Cochrane review, our search of the English-language medical literature identified reports on three open trials (Femiano *et al*, 2002, 2004a,b) of ALA as a treatment option for oral conditions. Two of these reports were on BMS and one was on dysgeusia (disorder of the sense of taste).

Femiano *et al* (2004a) assessed whether psychotherapy as a monotherapy, ALA as a monotherapy, or the two treatment modalities in combination were useful in managing BMS. They concluded that the maximum benefit was achieved with combination therapy and suggested that ALA may complement psychotherapy as an adjuvant therapy.

Femiano *et al* (2004b) also assessed the efficacy of ALA on two different groups of patients – 20 patients who had used tranquilizers for at least 6 months before the BMS diagnosis and 20 who had not. Of the 20 patients who had used tranquilizers, four patients reported a decided improvement, seven had a slight reduction in symptoms, two reported a worsening of symptoms, and seven had no change. Of the 20 patients who had not previously used tranquilizers, 11 had a complete resolution of symptoms, four had decisive improvement, three had a slight reduction in symptoms, and two had no change. These findings suggest that, for reasons not fully elaborated, ALA may be more effective in patients who have not previously been treated with psychoactive medications.

In an open crossover study, Femiano *et al* (2002), examined the use of ALA as a therapy for idiopathic dysgeusia. Of 22 patients using ALA, 46% achieved resolution and 91% achieved some symptomatic improvement; 36% of the 22 patients in the placebo group had some symptomatic improvement. When those in the placebo group crossed over to using ALA, 36% had marked improvement and 72% had some improvement in symptoms.

Our report is the first on a US population-based study of the efficacy of ALA. Many different ALA products are available without a prescription in the USA; some are monoingredient preparations, others may be compounded with vitamins. It is not clear from the reports of the six European trials on ALA use for BMS and dysgeusia whether ALA was used as a monoingredient preparation or in combination with other ingredients. Those researchers favored a product called Tiobec (Pharma Natura, Laborest, Italy). According to the electronic drug reference database Micromedex (Sweetman, in press), Tiobec is a multi-ingredient preparation containing vitamins in addition to ALA; Micromedex does not identify which vitamins are included.

The response to ALA among our cohort of patients with burning mouth is not as encouraging as the response rate reported for the European studies. However, the higher success rates described in those studies may be attributable to many factors. Although our results are not as impressive as those reported earlier, they do suggest that ALA may offer potential benefit, particularly to patients with a disorder whose treatment is challenging at best. ALA is inexpensive, safe, and well tolerated, so it certainly may have its place in the treatment of sore, burning mouth and can be added to the armamentarium of therapeutic interventions. Nonetheless, its supposed effectiveness may be the result of a substantial placebo effect. On the basis of our data, we could not definitively conclude that ALA is indeed an effective therapy for burning mouth but rather that it is worthy of further consideration and study.

Conclusions

Eleven (35%) of our 31 patients who actually used ALA derived symptomatic relief of BMS. These results are somewhat lower than those reported by other authors (range, 76–97%). Our study had a small number of patients, was retrospective in nature, used a subjective assessment of outcomes, included varying doses of ALA and durations of treatment, and even lacked uniformity in the ALA product that was used by the patients. Other authors have indicated that ALA produces a better response rate in certain subsets of patients and may also be used in a vitamin formulation. Better evaluation of the efficacy of ALA is required in larger, prospective, randomised, controlled, double-blind clinical trials.

Conflict of interest

None.

Author contribution

J.C.S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

All authors have given final approval of the submitted manuscript. The following authors have participated in the work and take responsibility for the whole content (J.C.S., A.J.B., L.A.D., and R.S.R.), contributed to conception and design (A.J.B., L.A.D., and R.S.R.), acquisition of data (J.C.S. and L.A.D.), analysis and interpretation of data (J.C.S., A.J.B., L.A.D., and R.S.R.), drafting of the manuscript (J.C.S.), critical revision of the manuscript for important intellectual content (A.J.B., L.A.D., and R.S.R.), administrative, technical or material support (J.C.S., A.J.B., and R.S.R.) and supervision (A.J.B., L.A.D., and R.S.R.).

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