

RESEARCH & APPLICATIONS

WHITE paper

Commentary by Howard E. Strassler, DMD

Practical interpretations of current investigations.

Effect of Bioactive B₁₂ in Adhering Discs on Aphthous Ulcers

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Recurrent aphthous ulcers (RAU), colloquially called canker sores, are one of the most common inflammatory conditions of the oral mucosa, affecting approximately 20% of the US population.¹ RAU is a common mucosal condition that consists of recurrent episodes of one or several rounded, shallow, painful oral ulcers at intervals of a few months to a few days with three typical presentations: (1) minor; (2) major; or (3) minor clusters (often called “herpetiform” but not related to clustered herpes ulcers).² Minor RAU is by far the most common presentation and manifests as round, clearly defined, small painful ulcers with shallow necrotic centers, raised margins and erythematous halos.³ They are localized most commonly to the unattached oral epithelium, specifically the buccal and labial mucosa, floor of the mouth, and edge of the tongue. The lesions typically heal within 10 to 14 days without scarring.^{3,4} In those individuals with recurring overlapping lesions, however, the problem can be quite troublesome. Most researchers who have attempted to estimate the occurrence of RAU conclude that about 20% of the US population suffers from the condition with sufficient severity to consult a physician, dentist, or pharmacist for treatment. Epidemiologic studies vary by region and the type of study cohort examined. Nonetheless, they suggest that the prevalence of RAU in the United States is between 5% and 60%.⁵ Population studies in various countries have found from 1.9% to 20% in the general population.³ Women are over-represented⁶ and whites are three times more likely to be affected than black people.⁷ Most estimates fall between 5% and 25%.^{1,3-5}

Lesions associated with recurrent aphthous stomatitis (RAS) are differentiated from RAS-like oral lesions arising from systemic abnormalities such as HIV infection, autoimmune disease (eg, lupus), food allergy (eg, gluten sensitivity), Crohn’s disease, drug insensitivity, pharyngitis, and cyclic neutropenia.^{2,4,8-10} For uncomplicated RAS, precipitating factors include genetic predisposition, local trauma, stress,

and nutritional deficiencies.^{2,3,11} Current treatments for RAS, regardless of etiology, include antimicrobial mouthwashes and local anesthetics which have not been shown to alter the recurrence or remission rates of sores,^{2,3,11} adhering dissolving discs that time release Glycyrrhiza extract (Canker Melts[®]—Orahealth)¹² and barrier cyanoacrylate formulations (Orabase[®] Sooth-N-Seal—Colgate Oral Pharmaceuticals)¹³ which have supportive research, and a variety of other over-the-counter (OTC) products that have not been adequately studied for efficacy.¹⁴ When OTC treatments are ineffective, topical and systemic steroids or thalidomide are often used. However, the costs, side effects, and toxicity of such treatments are often prohibitive.^{2,3,11} Laser ablation can provide short-term symptomatic relief and ulcer healing¹⁵ but is of very limited practical benefit.¹⁶

There is considerable literature suggesting that uncomplicated RAS may be associated with hematinic deficiency, specifically a deficiency in folic acid and vitamin B₁₂. In a recent controlled study of 143 patients experiencing recurrent aphthous stomatitis compared with 143 age- and gender-matched patients, 26.6% of aphthous subjects demonstrated B₁₂ deficiency in contrast to 12.6% of the controls.¹⁷ In another study, vitamin B₁₂ levels were assessed in 35 patients with recurrent aphthous ulceration and 26 healthy controls. B₁₂ levels were found to be significantly lower in the RAS subjects than in the controls, while significant differences were not found for the other assessed hematological factors.¹⁸ These studies, coupled with numerous other references,^{5,9,10,19} highlight the general assumption that vitamin B₁₂ plays a role in the etiology of some cases of recurrent aphthous stomatitis.

Given that B₁₂ deficiency may be the cause of ulcers in a subset of the population experiencing the condition, replacement therapy has been recommended.⁵ However, a number of studies suggest that the type of replacement therapy (eg, ingestion or injection) is a significant confounder of treatment outcome. For example, in

a randomized, double-blind, placebo-controlled study reported by Kolseth, Herlofson, and Pedersen involving Longo-Vital[®] (Pharmavita, Ltd, London, UK), an herbal-based ingested tablet enriched with vitamins (including B₁₂) and other trace elements, no difference was found between the herbal and placebo groups in terms of treatment outcome.²⁰ In an additional double-blind, stratified-randomized clinical case-control study performed over 6 months, no significant difference in treatment outcome was found between placebo patients and those using ingested replacement therapy based on a 50% reduction in the number of ulcers and days in pain—considered by the authors as clinically relevant.²⁰ Conversely, in a case study involving three subjects with aphthous, two of whom were deficient in B₁₂ and one with only marginal deficiency, it was found that injected doses (vs B₁₂ taken by ingestion) of high levels of cyanocobalamin seemed to reduce the incidence of ulcers.²¹ No published studies, to date, have attempted to assess the effectiveness of topical delivery of vitamin B₁₂ to the mucosal tissues or assess the commercially available bioactive form of B₁₂, methylcobalamin, for palliative or preventive treatment of recurrent aphthous ulcers.

Deoxyadenosylcobalamin is the main vitamin B₁₂ analogue found in a normal diet.²² The form of B₁₂ that is currently available in manufactured tablet form is cyanocobalamin. This latter compound (which is light stabilized by combining cobalamin with a cyano group) is not usable by the body until it has been converted in the liver or serum to a form that is bioactive, such as methylcobalamin or deoxyadenosylcobalamin.

Methylcobalamin and hydroxocobalamin have been shown to have effects on a number of conditions including peripheral neuropathy,²³⁻²⁵ allergy,²⁶ and methylmalonic acidemia and homocystinuria.¹¹ There is also evidence that methylcobalamin may affect immune function^{27,28} and may alter cellular function in other ways as well. For example, methylcobalamin

decreases mRNA levels of androgen-induced growth factor in androgen-dependent Shionogi carcinoma.²⁹ It has also been shown to attenuate the hypoxia/hypoglycemia or glutamate-induced reduction in hippocampal fiber spikes in vitro.³⁰ In an animal study assessing the effect of methylcobalamin on peripheral nerve structure, doses of 500 mcg/kg were delivered to diabetic rats for 16 weeks, with subsequent comparison of isolated nerves (from diabetic and nondiabetic animals) suggesting that methylcobalamin protected myelinated nerve density as well as fiber and axon size.³¹ Homocysteine (tHcy) concentrations (which have been linked to atherosclerosis) are also reduced by administration of methylcobalamin.³² Hydroxocobalamin attenuates effects of toxins.³³ For treatment of some diseases, hydroxocobalamin is effective where common vitamin B₁₂ (cyanocobalamin) is not.¹¹

DOUBLE-BLINDED, PLACEBO-CONTROLLED TRIAL

To assess the potential effect on RAS of bioactive methylcobalamin delivered once a day into the saliva, a randomized clinical trial (RCT) study was designed with a delivery vehicle that incorporated 500 mcg of methylcobalamin into a fully dissolving adhering disc (from Orahealth Corp, Bellevue, WA). From previous experimentation, it had been established that once placed in the mouth, the disc dissolved over 20 to 40 minutes. The disc ingredients, to which bioactive B₁₂ was added, consist of food polymers (hydrophilic gums), and xylitol for flavor. This formulation (with the bioactive B₁₂) was compared with a similar disc that contained only added food coloring.

Subjects were recruited with self-reported RAU who acknowledged having at least one lesion per month, absence of any known disease causing the ulceration, and who stated that they were not taking B₁₂ by injection or vestibular placement. The initial study involved 15 subjects, seven of whom received discs with 500 mcg methylcobalamin and eight

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B₁₂) is effective in reducing painful, minor recurrent aphthous ulcers. Perceived improvement is also significant. Although more active than placebo patients reported improvement in lesion duration and less frequent ulcers, the values were not statistically significant with this number of subjects. The descriptive data, however, suggests that there was perceived benefit with respect to the duration of the lesions and how frequently they were occurring in those using methylcobalamin B₁₂. Further, the data indicates that between 2 to 5 days of everyday use is required to achieve the full therapeutic benefit of disc use, with the data also suggesting that perceived benefit persists for about 3 to 7 days after disc use is discontinued.

The mechanism by which bioactive B₁₂ reduces pain and increases perceived improvement is not evident. A number of molecular and cellular mechanisms are possibly responsible for its therapeutic efficacy. Given placement in the mouth, absorption may occur through the mucosa as a surface effect but also through the intestinal epithelium secondary to swallowing. Direct topical effects may include enhanced peripheral nerve regeneration, localized neutrophil activation, an interaction with resident surface bacteria, or a combination of all of these effects. Systemic effects may include central nervous system activity (with psychological and physiological effects) and increased B₁₂ levels in cases of marginal or frank deficiency.

At this point we do not know whether a lesser dose of methylcobalamin would have been as effective as that provided. Further, these studies have not helped to define the upper dose that could have therapeutic benefit. However, given that there appears to be no upper safe limit for the use of methylcobalamin, the only drawback to using a higher dose than 500 mcg is cost.

If a dose is missed on one, two, or three days, it is not clear whether extra doses should be taken to make up for the missed doses or whether, when preventive treatment is initiated, one should subsequently commence with higher than normal doses. However, based on the above research, a reasonable use estimate is that when a person first starts using the discs, he or she should use three discs the first day to quickly boost the level of methylcobalamin in the mouth surface tissue cells. When a day is missed, it appears reasonable for a person to take two discs the next day. Given absence of data suggesting risk associated with upper levels of B₁₂, it would also appear reasonable for a person missing two or more days to use three discs the first day that treatment is subsequently resumed.

In conclusion, the above studies support the use of methylcobalamin, (Avamin[®] Melts[®]) in the management of uncomplicated recurrent aphthous ulceration.

COMMENTARY

Recurrent aphthous stomatitis (RAS) or recurrent aphthous ulcers (RAU) is a common condition, restricted to the mouth, that typically starts in childhood or adolescence as recurrent small, round, or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or gray floors. A positive family history of similar ulcers is common. This condition continues into adulthood. Our patients are relieved that the diagnosis of these uncomfortable oral ulcers is not cancer. The fact that these lesions recur and are uncomfortable creates the clinical challenge of providing our patients with a definitive treatment to relieve the symptoms over the 10 to 14 days that they exist. This paper provides an excellent overview of RAU with a focus on diagnosis and the current state-of-the-art in treatment. Also, this well-designed clinical research study provides another treatment that is easy for a patient to follow to provide relief. The data and analysis of data from these studies support the use of methylcobalamin (Avamin[®] Melts[®], Orahealth Corp, Bellevue, WA) in the management of uncomplicated recurrent aphthous ulceration.

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