

ZINC SULFATE IN TREATMENT OF THE PATIENTS WITH RECURRENT APHTOUS STOMATITIS

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SUMMARY: Twenty-six patients with recurrent aphtous stomatitis were studied with respect to zinc and copper deficiency. Their mean serum zinc levels before treatment was $78.23 \pm 2.64 \mu\text{g/dl}$ and after treatment $100.31 \pm 3.56 \mu\text{g/dl}$ ($p < 0.05$). Zinc content of 10^{10} erythrocytes was 11.35 ± 0.41 before and $13.54 \pm 0.50 \mu\text{g}$ after treatment ($p < 0.05$) while serum copper levels were maintained almost at the same level ($p > 0.05$). Of the total series, before treatment, serum Zn levels in 20 patients, serum copper levels in 5 patients, and Zn contents of 10^{10} erythrocytes in 18 patients were found below normal levels. Following one, two, and three months of treatment serum Zn levels and Zn contents of 10^{10} erythrocytes of patients rose parallel to the improvement in clinical findings. A significant remission was observed after the 3rd month of treatment in 22 (84.6%) of 26 patients. The differences between pre-treatment and of monthly evaluation following treatment in mean serum Zn levels and Zn contents of 10^{10} erythrocytes were statistically significant ($p < 0.05$).

Key Words: Recurrent aphtous stomatitis, Serum Zn level, Serum Cu level, Erythrocyte zinc.

INTRODUCTION

Recurrent aphtous stomatitis (RAS) is a chronic inflammatory disease of man characterized by painful, recurrent ulcerations of the oral mucosa. Approximately 20 percent of the general population will have this disease during a period of his life (1-7). Despite the fact that the clinical, etiologic, histopathologic and therapeutic aspects of this disease has been extensively investigated, the primary cause has as yet not been established. Mainly two distinct groups of factors were however claimed to be important in etiology of the aphtous ulcers. The first group consists of bacteria and viruses and the second is com-

posed of endogenous precipitating causes such as hormonal changes systemic diseases (3, 5,7). Contribution of these factors, if any, however has never been sufficiently clarified (1,2,4,8-11). This uncertainty has necessarily affected treatment several modalities of which have been proposed to eliminate recurrence and to reduce duration of aphtous ulcerations. Additional research on the etiology, pathogenesis and treatment of RAS is therefore needed (1,3,5,7,10,12-15).

The purpose of this study is to report the results of systemic ZnSO_4 and CuSO_4 treatment in patients with RAS.

MATERIALS AND METHODS

Twenty-six consecutive out patients between ages 4 and 75 (mean age 34.21) who complained only from recurrent aphtous stomatitis were included in this study. Twenty one of the patients were male and 5 were female.

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The diagnosis of RAS was made by detailed history and clinical characteristics of the oral ulcers. The onset, distribution, number, duration of ulcers, and existence as well as severity of localized pain were noted. The patients who had bullous or traumatic ulcers, acute ulcerative gingivitis, Reiter's syndrome, Behcet's syndrome, and gastrointestinal or endocrine system disorders were not included in the series reported in this communication. The patients were not using any other medication during the time they remained under this specified therapy.

A venous blood sample was obtained from each patient after a night's fasting before starting treatment. Serum Zn and Cu levels and Zn contents of 10^{10} erythrocytes were measured using atomic absorption spectrophotometer (Perkin-Elmer Model 103) (16). Routine blood and urine analyses were done.

Clinical and hematological controls were repeated every month. Changes in the number and duration of oral ulcers and the severity of the pain were noted. Each patient acted as his or her own control.

According to these results all the patients were given 50-200 mg once of twice per day of $ZnSO_4 \cdot 7H_2O$ molecule and 0-5 per day of $CuSO_4 \cdot 5H_2O$ molecule orally during or after meals.

The results before and after the treatment were evaluated statistically.

RESULT

Clinical Findings

Before the treatment, the durations of apthae ranged from 2 months of 30 years (mean 8.5 years) and activity periods of individual ulcers between 5 to 30 (mean 15.3) days. The ulcers were usually multiple in number and localized at different areas of the oral cavity, mainly on the tongue and lips, and to a lesser extent on the gums, on the mucosa of the cheeks and on the uvula. All the patients complained of severe localized pain.

During the first month following the treatment a reduction in the number of ulcers and shortening of the activity periods were observed. They were less painful and smaller in size. Complete remission was observed after 3

months of treatment in 22 (84.6%) of 26 patients. In the remaining four (15.4%) recurrences were observed lesions however were also of shorter duration, smaller in size and the periods between the episodes had been significantly prolonged.

Serum Zinc Levels

Before the treatment serum Zn levels in 20 of 26 (76.9%) patients with RAS were below normal values and the mean serum Zn level of 26 patients was found to be (78.28 ± 2.64) . The normal values of 22 healthy persons of comparable age was 93.2 ± 1.8 (S.E.). Following the first month of treatment, serum Zn levels of patients rose parallel to the improvement in clinical findings. After 3 months of treatment serum Zn levels of 5 patients only (19%) still remained below normal value. The serum Zn levels of 26 patients were found $(93.31 \pm 3.20, 91.23 \pm 3.74$ and $100.31 \pm 3.56)$ one, two and three months after treatment respectively. The differences between pretreatment and of monthly evaluations following treatment were statistically significant ($p < 0.05$, Table 1). The difference between 1st and 2nd months however was not statistically significant ($p > 0.05$).

Zn Content of 10^{10} Erythrocytes

Before treatment, Zn contents of 10^{10} erythrocytes of 18 patients were below normal values (69.2%) and the Zn content of 10^{10} erythrocytes of all the patients combined were found to be $(11.35 \pm 0.41 \mu g)$. They returned to normal values $(12.61 \pm 0.37, 12.95 \pm 0.45$ and $13.54 \pm 0.50)$ one, two and three months following treatment respectively.

The differences between pre-treatment and of each month following treatment, were statistically significant ($p < 0.05$, Table 1).

Serum Cu Levels

Before the treatment, serum levels of 5 patients (19%) were below normal value, and the mean serum Cu level of

Table 1: The mean serum Zn, serum Cu levels and Zn contents of 10^{10} erythrocytes before and after treatment.

	Before treatment	After treatment		
		1st month	2nd month	3rd month
Serum Zn ($\mu g/dl$) n:26	$78.23 \pm 2.64^*$	$93.31 \pm 3.20^*$	$91.23 \pm 3.74^*$	$100.31 \pm 3.56^*$
Serum Cu ($\mu g/dl$) n: 26	98.77 ± 3.78	100.46 ± 4.81	104.85 ± 4.10	102.92 ± 3.68
Zn of 10^{10} erythrocyte (μg) n: 26	$11.35 \pm 0.41^*$	$12.61 \pm 0.37^*$	$12.95 \pm 0.45^*$	$13.54 \pm 0.50^*$

\pm standard deviation of the mean

* $P < 0.05$ compared to the value of before treatment.

all the patients was found to be normal (98.77 ± 3.78). Normal values of 22 healthy persons of comparable age was 103.2 ± 2.4 (S.E.). During the months following treatment, the mean serum Cu levels remained within normal limits ($p > 0.05$, Table 1).

DISCUSSION

The etiology of recurrent aphtous stomatitis still remains obscure (5-10). Attempts to prevent recurrences or to alleviate the accompanying suffering from, aphtous stomatitis, many empirical treatments have been proposed with therefore no permanent success (17). We observed healing of the aphtous ulcerations of in the oral cavity of patients who were for other conditions given zinc sulfate treatment. It was then decided to try zinc treatment in a series of patients who had no other ailments. In fact use of zinc sulfate in promotion of wound healing and maintenance of epithelial integrity seemed to agree with its possible use in the treatment and prevention of RAS (18-24).

Battistone and associates (25), McCray and co-workers (26), and Mesrobian and Shklar (27) have shown improvement in oral wound healing rates in hamster and guinea-pigs following administration of zinc sulfate or zinc cysteamine-N-acetic acid. Furthermore previous reports (17,24,28) indicate that systemic zinc supplementation causes an improvement or even remission in selected patients with RAS.

Merchant and associates have reported a marked reduction in number of ulcers, of their sizes and activity periods, especially of pain using a total of 660 mg of zinc sulfate per day in a series of 32 patients with recurrent aphtous ulcerations (RAU). They suggested that RAU may be due to several causes, one of which may be a local or general deficiency of zinc or a defect in metabolism, perhaps at the cellular level (24). Merchant in their series serum zinc levels of 17 patients are reported. Of these 8 patients presented with zinc levels above 110 $\mu\text{g/dl}$ and 9 below. Those of the second group reported improvement and three reported complete remission. The last 3 patients however suffered recurrence few weeks after cessation of treatment (24). Serum copper levels of these patients were not however determined.

Wray and his group observed no therapeutic effects with systemic zinc sulfate over a 3-month period in a double-blind crossover trial involving twenty patients. Their lack of success was considered secondary to selection of patients (17) whose pretreatment serum zinc levels were not reduced. They apparently did not follow its possible changes while under therapy.

In our study before the treatment, serum Zn levels in 20 patients, serum Cu levels in 5 patients and Zn contents of 10^{10} erythrocytes in 18 patients were found below normal values. Oral zinc treatment using 50-200 mg of zinc sulfate three times daily appeared to alleviate the symptoms in a great majority of our patients as documented by healing or reduction in the size and number of the ulcers and their activity periods as well as disappearance of pain.

Complete remission was observed after 3 months of treatment in 22 of 26 patients. In the remaining four patients who still had recurrences while under treatment since three months the lesions of the recurrent episodes were, however of shorter duration, smaller in size and were separated with wider periods free of symptoms. It is also noteworthy that these four patients were mean while completely free of pain it should also be stressed here that the clinical improvement occurred simultaneously with the return of reduced zinc levels to normal.

As observed in Table 1 zinc deficiency shows a closer correlation with development of aphtous stomatitis. Further consideration of Table 1 discloses that return of serum and erythrocyte zinc levels towards normal is followed by disappearance of RAS in almost all cases.

Discontinuation of the drug was followed by recurrence of the symptoms in almost all cases early in the course of therapy. This was correct for some cases even after months of oral zinc supplementation. This response was therefore utilized as a method of control for the influence of zinc sulfate treatment and it obviated further control studies for its influence.

Since zinc deficiency was observed in all of these patients it is easy to understand the reason for oral zinc administration. However the same can not be told for copper supplementation. It is interesting from this respect that copper even though may be at normal levels before treatment, it is frequently reduced following a few days of oral zinc treatment. What is more interesting is the observation that following institution of copper deficiency the original symptoms recur. In order to prevent this we adopted the method of routine copper supplementation of patients from the beginning or oral zinc therapy. In innumerable instances we have been able to prevent development of copper deficiency while we restore serum zinc levels to normal (29-31).

An interesting consideration is whether copper deficiency may also lead to development of aphtous ulcerations of the month. No definite answer could at present be given to this important question. We may even consider the possibility of other trace elements playing a role in the

ethiopathogenesis of this unique disorder. It is furthermore observed that in most of our cases serum copper levels were within normal values at the beginning of the treatment. In five cases they were somewhat reduced. It is important to note as the patients responded to treatment with zinc and copper levels in serum both returned to normal. Simultaneously the patients improved clinically.

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