Recurrent herpes labialis: a pilot study of the efficacy of zinc therapy

F. Femiano¹, F. Gombos¹, C. Scully²

¹Stomatology Clinic, II University of Medicines and Surgery, Naples, Italy; ²Eastman Dental Institute, University College London, London, UK

BACKGROUND: The objective of this study was to investigate the effect of zinc on recurrent herpes labialis. MATERIALS/METHODS: Twenty patients (12 females; median age 26.6 years) with a history of recurrent herpes labialis >6 episodes each year were treated with systemic zinc sulphate 22.5 mg twice daily for the months of February, March, September and October. All patients were followed for 12 months.

RESULTS: Herpetic lesions reduced to <4 episodes (average 3) for the 12 months and the duration was <7 days for each episode (average 5.7).

CONCLUSIONS: Systemic zinc sulphate appeared to reduce both the number of episodes and the time to recovery of herpes labialis.

| Oral Pathol Med (2005) 34: 423-5

Keywords: herpes; recurrent herpes labialis; zinc

Introduction

Herpes labialis is one of the most prevalent and clinically obvious diseases. Recurrence is a common characteristic (1, 2).

After the initial infection, which is often an acute stomatitis, the causal micro-organism, herpes simplex virus (HSV) type 1, remains latent in the trigeminal ganglion and may be reactivated by stress, fever, upper respiratory tract infections, ultraviolet light, trauma and immune incompetence but the condition is variable and unpredictable in most patients, as is the extent and duration of each attack (3).

The classical lesion of recurrent herpes labialis comprises a prodrome and erythema, followed by papular, vesicular and ulcerative stages and, finally, there is crusting and healing over 8-14 days. Active virus is present throughout the vesicular stage, and therefore,

Correspondence: Dr Felice Femiano, Via Francesco Girardi 2, S. Antimo (NA), 80029, Italy. Tel: + 39 081-8304248. Fax: + 39 081-5051524. E-mail: femiano@libero.it

Accepted for publication February 28, 2005

treatment to arrest the viral replication should theoretically be effective during that part of the development of the classic lesion (4).

Recurrent attacks are usually shorter and less painful than the original attack of stomatitis and for many immunocompetent patients, herpes labialis presents little more than an unaesthetic nuisance (5). However, for people whose recurrent herpetic disease occurs six or more times per year, it can be incapacitating, sometimes patients having cold sores for up to 60 days each year (6).

Although antiviral agents, including aciclovir, may be effective against recurrent herpes labials, most are expensive, may have toxicity or side effects, and can promote viral resistance (7-10). Consequently, a safer and more effective method to prevent, eliminate or substantially reduce recurrences should be of considerable importance.

In this study we have considered the effectiveness of preventive therapy using systemic zinc sulphate (5).

Patients and methods

The study group consisted of 20 HIV-seronegative patients (12 females; median age 26.6 years), who had clinically documented herpes labialis, >6 episodes each year for three or more years, normal full blood picture, serum immunoglobulin levels and lymphocyte T4/T8 subsets. The median duration of episodes to cessation of pain was 10.8 days.

All subjects were informed of the purpose and local ethical committee approval was obtained.

All patients were asked to swallow 22.5 mg zinc sulphate granules dissolved in a glass of water twice daily, each day, for the months of February, March, September and October over 1 year. Patients were asked to refrain from any other treatments for their lesions.

The herpetic lesions were clinically monitored, instructing the patients to recognize and to record as the initial lesion the erythemato-vescicular stage and as the final stage, the spontaneous loss of the crust.

All patients were clinically followed up over a 12month observation period.

Results

474

After 12 months, and the regimen of zinc sulphate, the herpetic lesions had reduced to <4 episodes (average 3) and the duration was <7 days (average 5.7) (Table 1).

The data were evaluated by ANOVA test.

Discussion

This study suggests that systemic zinc may reduce the number of episodes of herpes labialis, as well as the times of recovery. Clearly placebo-controlled randomised double blind studies are now required to explore the validity of these observations.

The body contains 2–3 g of zinc (Zn), found in high concentrations in the prostate gland, testes and semen, and also present in bones, teeth, hair, skin, liver, muscle and leukocytes. About one third of the 100 μ g/dl (15.3 μ mol/l) of zinc found in plasma is attached loosely to albumin, and about 2/3 is firmly bound to globulins (11).

Zinc has several roles in metabolism. There are >100 zinc metalloenzymes, including a large number of nicotinamide adenine dinucleotide (NADH) dehydrogenases, RNA and DNA polymerases, and DNA transcription factors as well as alkaline phosphatase, superoxide dismutase and carbonic anhydrase.

Meat, liver, eggs and seafood (especially oysters) are good sources of zinc. Dietary intake of zinc by healthy adults varies from 6 to 15 mg/day, and absorption is about 20%. The RDA is 0.2 mg/kg/day for adults (12– 14).

Zinc deficiency can have several effects but clinical assessment of mild zinc deficiency is difficult because many of the signs and symptoms are non-specific. Nonetheless, if a malnourished person has a borderline-low plasma zinc level, is subsisting on a high fibre and phytate diet containing whole-grain bread (which reduces zinc absorption), and has reduced taste sensitivity, an impaired lymphocyte response to mitogens, and reduced gonadal hormone function, then zinc deficiency should be suspected, and treatment with zinc supplements (15–25 mg/day) should be tried (15). Acrodermatitis enteropathica is a more severe childhood form of zinc deficiency, which manifests with periorificial (oral, anal, genital) and acral dermatitis, diarrhoea, behavioural and mental changes, neurological disturbances and secondary bacterial and fungal infections, though it has not been reported to pre-dispose to herpetic lesions.

Biochemical signs associated with zinc deficiency include decreased levels of plasma zinc [$<70 \mu g/dl$ ($<10.7 \mu mol/l$)], alkaline phosphatase, alcohol dehydrogenase in the retina (which accounts for night blindness), and plasma testosterone as well as impaired T-lymphocyte function, decreased collagen synthesis (resulting in poor wound healing), and decreased RNA polymerase activity in several tissues (11, 15).

The zinc has capacity for the safe control of viruses by cell-mediated immunity stimulation. The T-cell lymphocyte response is the basis of cellular-mediated immunity (CMI). The CMI is vitally important in protection against virus, fungal and protozoan infections, as well as against malignant and autoimmune disease (16).

Zinc appears to increase number of helper or effector T-cells, or precursors of antibody forming cells or increased suppressor cell activity (17). Zinc ions stimulate lymphocyte DNA synthesis within a few days and approximately 10–40% of lymphocytes are transformed into lymphoblasts. Additionally zinc-8 hydroxyquino-

Table 1 Characteristics of study group of patients with recurrent herpes labialis before and after use of zinc

No. patient	Age	Sex	No. episodes/year before use of zinc	Average duration (days) of episodes of RHL in absence of topical antiviral therapy	No. episodes/year after use of zinc	Average durations of episodes of recurrent herpes labialis after use of zinc
1	32	Male	6	9	3	4
2	14	Male	5	12	2	5
3	28	Female	8	14	4	7
4	15	Female	6	12	3	6
5	30	Female	9	10	4	5
6	27	Male	7	10	3	5
7	35	Female	6	13	2	6
8	21	Female	5	14	3	5
9	29	Female	8	8	3	6
10	19	Male	6	10	2	7
11	24	Male	7	9	4	6
12	29	Female	7	10	3	6
13	33	Female	8	8	4	4
14	36	Male	9	11	3	6
15	32	Female	5	13	2	6
16	18	Female	7	12	3	7
17	22	Male	8	9	4	6
18	24	Female	6	9	3	4
19	34	Male	7	11	3	6
20	31	Female	8	12	4	7

ANOVA test: P < 0.0001.

line unsaturated complexes are stimulatory to lymphocyte mitosis in animals and at least two mechanisms appear to exist for zinc to stimulate lymphocytes in animal models (18).

In humans, one protein, transferrin, is vital to CMI in that only transferrin bound zinc is functional in the T-cell lymphocyte. Since transferrin in the human is only 30% iron saturated, substantial zinc transport capacity for immune function is normally available. Clearly, a nutritional deficit that induces a loss or significant reduction in transferrin synthesis would cause both anaemia and primary immunodeficiency. Interferon and transferrin concentrations are reduced in those nutritional deficiencies, such as zinc, that interfere with protein synthesis (19–22).

References

- 1. Glick M. Clinical aspects of recurrent oral herpes simplex virus infection. *Compend Contin Educ Dent* 2002; 23: 4–8.
- 2. Huber MA. Herpes simplex type-1 virus infection. *Quintessence Int* 2003; **34**: 453–67.
- 3. Sciubba JJ. Recurrent herpes labialis: current treatment perspectives. *Compend Contin Educ Dent* 2002; 23: 9–12.
- Siegel MA. Diagnosis and management of recurrent herpes simplex infections. J Am Dent Assoc 2002; 133: 1245–9.
- 5. Whitley RJ. Herpes Simplex Virus in Children. *Curr Treat Options Neurol* 2002; **4**: 231–237.
- 6. Spruance SL, Kriesel JD. Treatment of herpes simplex labialis. *Herpes* 2002; **9**: 64–9.
- Jensen LA, Hoehns JD, Squires CL. Oral antivirals for the acute treatment of recurrent herpes labialis. *Ann Pharmacother* 2004; 38: 705–9.
- 8. Baker D, Eisen D. Valacyclovir for prevention of recurrent herpes labialis: 2 double-blind, placebo-controlled studies. *Cutis* 2003; **71**: 239–42.
- Femiano F, Gombos F, Scully C. Recurrent herpes labialis: efficacy of topical therapy with penciclovir compared with acyclovir (aciclovir). Oral Dis 2001; 7: 31–3.
- Straus SE, Seidlin M, Takiff K, Jacobs D, Bowen D, Smith HA. Oral acyclovir to suppress recurring herpes simplex

virus infections in immunodeficient patients. Ann Intern Med 1984; 100: 522-4.

- 11. Wieringa FT, Dijkhuizen MA, West CE. Iron and zinc interactions. *Am J Clin Nutr* 2004; **80**: 787–8.
- Bick MJ, Carroll JW, Gao G, Goff SP, Rice CM, MacDonald MR. Expression of the zinc-finger antiviral protein inhibits alphavirus replication. *J Virol* 2003; 77: 11555–62.
- Carrington-Lawrence SD, Weller SK. Recruitment of polymerase to herpes simplex virus type 1 replication foci in cells expressing mutant primase (UL52) proteins. *J Virol* 2003; 77: 4237–47.
- Inman M, Zhang Y, Geiser V, Jones C. The zinc ring finger in the bICP0 protein encoded by bovine herpesvirus-1 mediates toxicity and activates productive infection. *J Gen Virol* 2001; 82: 483–92.
- 15. Lim NC, Freake HC, Bruckner C. Illuminating zinc in biological systems. *Chemistry* 2004; 14: 31–5.
- Fraker PJ, King LE. Reprogramming of the immune system during zinc deficiency. *Annu Rev Nutr* 2004; 24: 277–98.
- Bogden JD. Influence of zinc on immunity in the elderly. J Nutr Health Aging 2004; 8: 48–54.
- Ribeiro RC, Sales VS, Neves Fde A, Draibe S, Brandao-Neto J. Effects of zinc on cell-mediated immunity in chronic hemodialysis patients. *Biol Trace Elem Res* 2004; 98: 209–18.
- Raqib R, Roy SK, Rahman MJ, Azim T, Ameer SS, Chisti J, Andersson J. Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with shigellosis. *Am J Clin Nutr* 2004; **79**: 444–50.
- Logan HL, Lutgendorf S, Hartwig A, Lilly J, Berberich SL. Immune, stress, and mood markers related to recurrent oral herpes outbreaks. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86: 48–54.
- Arens M, Travis S. Zinc salts inactivate clinical isolates of herpes simplex virus in vitro. J Clin Microbiol 2000; 38: 1758–62.
- 22. Bansal R, Tutrone WD, Weinberg JM. Viral skin infections in the elderly: diagnosis and management. *Drugs Aging* 2002; **19**: 503–14.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.