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Lysine Prophylaxis in Recurrent Herpes Simplex Labialis: A Double-blind, Controlled Crossover Study

N. Milman, J. Scheibel and O. Jessen

Department of Infectious Diseases M 7722, Rigshospitalet, DK-2200 Copenhagen N, Denmark

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Abstract. L-lysine has an inhibitory effect on the multiplication of herpes simplex virus in cell cultures. We have evaluated the prophylactic effect of L-lysine monohydrochloride 1 000 mg daily on recurrent herpes simplex labialis in 65 patients in a double-blind, placebo-controlled, crossover study. After 12 weeks of lysine treatment the patients shifted to placebo treatment for a similar period. On the whole, lysine prophylaxis had no effect on the recurrence rate of herpes simplex. However, significantly more patients were recurrence-free during lysine than during placebo treatment ($p = 0.05$), suggesting that certain patients may benefit from prophylactic lysine administration. In the herpes lesions described, lysine had no effect on the rate of healing or on the appearance of the lesions at their worst.

Key words: Herpes labialis, drug therapy; Lysine

The multiplication of herpes simplex virus (H.S.V.) in cell cultures is inhibited by high concentrations of the amino acid L-lysine in the culture medium (6). In a previous therapeutic study (3) we demonstrated that lysine had no effect on the healing rate of recurrent herpes simplex labialis. In the recurrent herpetic lesion, virus multiplication begins in the prodromal stage and is maximal during the following 24 hours, whereafter it declines rapidly (5). Therefore, any treatment must be initiated immediately at the onset of the first symptoms. These circumstances motivated an evaluation of the prophylactic effect of lysine in recurrent H.S.V. infections.

PATIENTS AND METHODS

All subjects were otherwise healthy volunteers with at least three perioral and/or prolabial herpes simplex episodes in the preceding 12 months. The diagnosis was in some cases based upon the observation of lesions, and in the remaining cases upon a thorough history.

A total of 79 patients were initially admitted to the study; 14 did not complete the investigation and were excluded. The final material comprised 65 patients (52 females, 13 males) aged 16–73 years (median 36 years).

The trial was conducted as a double-blind, placebo-controlled, crossover study. At the first visit the patient was given a questionnaire and tablets containing 500 mg L-lysine monohydrochloride or starch powder (placebo). The patients were instructed to take one tablet twice daily during the entire study. Every second patient started with lysine and alternate patients with placebo. Initial treatment continued for 12 weeks, whereafter the patients shifted without interruption to the alternative treatment for the following 12 weeks. During treatment the patients recorded the duration and course of their herpes simplex recurrences on the questionnaires which, together with residual tablets, were returned by mail every 4th week. In due course a fresh issue of tablets and a new questionnaire were dispatched to the patients.

The start of the episode was defined as the appearance of burning, itching, tingling (prodrome) and/or erythema. The lesion was considered healed when the crust had been discharged and all discomfort and swelling had disappeared; residual erythema could still be present. A new lesion at a non-contiguous site was considered part of the episode when appearing before the initial lesion had healed.

Table I. *Number of herpes simplex recurrences during a 12-week prophylactic treatment with lysine (L) and placebo (P) in a crossover study*

	Patients starting with L ($n=31$)	Patients starting with P ($n=34$)	Total ($n=65$)
Total no. of recurrences during L treatment	45	46	91
Median and range	1 (0–4)	1 (0–6)	1 (0–6)
Total no. of recurrences during P treatment	38	66	104
Median and range	1 (0–4)	2 (0–6)	1 (0–6)

The patient was instructed to classify the lesion when judged to be at its worst according to the following scale: (1) itching, burning, tingling or tenderness but no visible lesion; (2) erythema with induration (papule) and/or vesicles without exudation; (3) vesicles with exudation and/or crust, lesion 15 mm or less, measured along the largest diameter; (4) vesicles with exudation and/or crust, lesion greater than 15 mm.

Statistical comparisons were made using the chi-square test and the sign test.

RESULTS

The numbers of herpes simplex recurrences during the trial are shown in Table I. Patients initially treated with lysine had 45 recurrences during lysine and 38 recurrences during placebo treatment. Patients initially treated with placebo had 66 recurrences during placebo and 46 recurrences during lysine treatment. The total number of recurrences during lysine treatment was 91, and during placebo treatment 104. None of these differences were statistically significant.

Table II describes the patient material according to the presence or absence of recurrences in relation to treatment. Fourteen patients had *no* recurrences during lysine treatment (but recurrences during placebo treatment), whereas 4 patients had *no* recurrences during placebo treatment (but recurrences during lysine treatment). This difference is at the limit of significance (sign test $p=0.05$).

There were no significant differences between lysine and placebo treatment series as regards the rate of healing and the appearance of the recorded herpes lesions at their worst.

In the lysine treatment series, 20 patients returned 272 tablets, and in the placebo treatment series 18 patients returned 275 tablets, i.e. in both series 2.5% of the number of tablets issued was returned.

DISCUSSION

Tankersley (6) demonstrated that H.S.V. multiplication was reduced in cell cultures when the

Table II. *Recurrence pattern of herpes simplex in 65 patients during prophylactic treatment with lysine (L) and placebo (P) in a crossover study*

	Patients starting with L ($n=31$)	Patients starting with P ($n=34$)	Total ($n=65$)
Patients having *no* recurrences during L treatment (but recurrences during P treatment)	5	9	14
Patients having *no* recurrences during P treatment (but recurrences during L treatment)	2 n.s.	2 n.s.	4 $p=0.05$
Patients having recurrences during *both* L and P treatment	20	23	43
Patients having *no* recurrences during L and P treatment	4	0	4

medium contained high concentrations of L-lysine and low concentrations of L-arginine, and suggested that a high lysine/arginine ratio was associated with poor conditions for virus growth.

In our previous double-blind, placebo-controlled therapeutic trial on recurrent herpes simplex labialis (3), lysine 1 000 mg daily for 5 days had no effect on the rate of healing of the episodes.

Griffith et al. (1), in an uncontrolled study, observed the beneficial effect of long-term treatment with lysine 300–1 000 mg daily on patients with recurrent cutaneous and labial herpes simplex.

The present study demonstrates clearly that lysine prophylaxis with 1 000 mg daily has no effect on the rate of healing or on the course of herpes labialis. Furthermore there is no unequivocal effect on the frequency of recurrences, although the interpretation of these results is somewhat more complicated. In patients initially treated with placebo there was a tendency towards fewer recurrences during subsequent lysine treatment (Table I). Also, patients initially treated with lysine had a lower number of recurrences on placebo treatment than had patients initially treated with placebo. Theoretically this could be attributed to a prophylactic long-term effect of lysine. However, analysis of the data does not support such an interpretation; of the 38 recurrences recorded during placebo treatment after crossover (Table I), 15 occurred within the first 4 weeks, 9 within the second 4 weeks and 14 within the third 4 weeks after lysine withdrawal, the differences being insignificant.

Significantly more patients were recurrence-free during lysine than during placebo treatment (Table II). This finding is probably accidental, but might also suggest an effect of lysine in some of the patients.

As demonstrated in earlier studies (2, 3, 4) there is a large placebo response in recurrent herpes simplex, presenting a considerable pitfall to clinical trials. Also, due to the great inter- and intra-individual variations in the frequency and course of recurrent herpes, evaluation of a prophylactic treatment presents great investigational problems; it requires large patient materials, long observation periods and makes the employment of double-blind, controlled trials absolutely necessary.

To sum up, lysine had no significant prophylactic effect, either on the duration or on the recurrence rate of herpes simplex labialis. However, the results suggest that certain patients may benefit from such treatment, and further investigations are indicated to clarify this hypothesis.

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Topical Treatment of Penile Condylomata Acuminata with Colchicine at 48–72 Hours Intervals

Geo von Krogh and Ann-Kerstin Rudén

Department of Dermatology, Södersjukhuset, S-10064 Stockholm 38, Sweden

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Abstract. We previously demonstrated that 8% solutions of colchicine in ethanol eradicated penile warts in 36% of patients after a single application and in an additional 12% after a second application performed at least a week after the first. In the present study only 30% of 115 men were cured when penile warts were painted twice at intervals of 48 hours with 2% solutions and 72 hours with 4% and 8% solutions of colchicine. The lack of additive therapeutic effect accruing from the second application and the high frequency of intolerable side effects when using the latter treatment program indicate that this regimen is unsuitable for condylomata therapy.

Key words: Condylomata acuminata; Topical drug therapy; Colchicine