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Topical treatment of recurrent mucocutaneous herpes with ascorbic acid-containing solution

T. Hovi [a,*], A. Hirvimies [b], M. Stenvik [a], E. Vuola [c], R. Pippuri [c]

[a] *Enterovirus Laboratory, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki, Finland*
[b] *Suomen Astra Oy, Masala, Finland*
[c] *Central Military Hospital, Helsinki, Finland*

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Abstract

We carried out a randomized double-bind, placebo-controlled clinical trial on the topical treatment of recurrent mucocutaneous herpes with a strong water solution of Ascoxal®, an ascorbic acid-containing pharmaceutical formulation with mucolytic and non-specific antimicrobial activities. The lesion was firmly pressed with a cotton wool pad soaked in drug solution 3 times for 2 min with 30-min intervals on the first day only. Evaluation of the effects was by daily recordings of several different symptoms, including the presence and severity of erythema, induration, papulae or vesicles and scab by both the patient and a trained nurse, and by virus culture. Fourteen episodes with active treatment and 18 with the placebo were analyzed. According to the patients' records, the active treatment resulted in a significantly smaller cumulative number of days with scab ($P < 0.01$), or with any remaining symptom ($P < 0.02$) and significantly fewer occasions of worsening of any symptom after the treatment ($P < 0.05$). According to the nurse's records, the persistence of scabs was significantly shorter in the active treatment group (means 3.4 vs 5.9 days, $P = 0.03$). Virus culture after the first day of treatment yielded herpes simplex virus significantly less frequently in the active treatment group than in the placebo group ($P < 0.01$). In conclusion, a brief treatment with this ascorbic acid-containing preparation resulted in statistically significant clinical and antiviral effects, which calls for further and more extensive studies with a more intensive treatment schedule.

Keywords: Mucocutaneous herpes; Recurrence; Herpes labialis; Topical treatment; Herpes simplex virus; Ascorbic acid

* Corresponding author. Fax: +358 (47) 44355.

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1. Introduction

Recurrent mucocutaneous non-genital herpes is a common disease with an usually benign natural course. However, in a remarkable proportion of patients, it is painful and significantly affects normal life. Specific antiviral compounds such as acyclovir and idoxuridine in certain formulations have been reported to have definite antiviral and some clinical effects (Spruance et al., 1990a,b). However, the actual benefit to the patient often remains rather marginal and, clearly, more effective modes of treatment are desirable.

Ascoxal® is an old pharmaceutical preparation marketed in the Scandinavian countries since the 1960s as an oral mucolytic and prophylactic agent against gingivitis. According to the manufacturer's data files, it has documented antibacterial, antimycotic and antiviral (vaccinia and poliovirus) activity (Wahlqvist, 1958). Several years ago one of us (A.H.) decided to try topical Ascoxal treatment for her own herpes labialis and experienced an apparently facilitated healing of the lesions. Similar observations were later made by several family members or other close contacts of the authors. According to this subjective and anecdotal experience, treatment with Ascoxal was needed only during the first day of the disease, and the healing was often rather rapid.

We report here a placebo-controlled double-blind trial on topical treatment of recurrent mucocutaneous non-genital herpes with Ascoxal solution.

2. Patients, materials and methods

2.1. Patients

Patients who volunteered for the trial were obtained from the staff of the National Public Health Institute (KTL) and the Central Military Hospital (KSS), Helsinki. A nurse at the occupational health clinic of KSS carried out a structured interview of previous herpes history of the volunteers, and gave advice to the patients with regard to the topical treatment and filling in the follow-up forms. The first episode after enrolment was usually used for this training. Patients with recurrent non-genital herpes without other skin disease, who gave an informed written consent were enrolled in the study.

The Ethical Committee of the National Public Health Institute and a National Board for Clinical Drug Trials reviewed the study plan before the onset of the trial.

2.2. General design of the study

According to the original protocol, the study was to consist of two parts, A and B. In part A, the treatment was nurse-initiated. After onset of prodromal or visible symptoms the patient contacted the nurse as early as possible for the pretreatment assessment. At this stage the patients were given a consecutive number that determined, in a randomized order and double-blind manner, the treatment schedule of two forthcoming successive episodes of the patient to be active–active, active–placebo, placebo–active or

placebo–placebo. Only those episodes were included in which the patient was seen by the nurse within 24 h of onset of first symptoms of the episode. After two treated episodes in part A, the patients were designated to proceed to part B and given the drugs, active or placebo, in a randomized manner, for patient-initiated treatment of the next episode. The patients were told to contact the nurse as soon as possible for the first post-treatment evaluation of the lesion. Analysis of results was planned to be based on pairwise observations in part A, and on between-all-episodes comparisons combining parts A and B. Several episodes suitable for part A were missed because of onset during week-ends or other days-off. Therefore, and in order to be able to collect sufficient data before the expiry date of the drugs, we modified the protocol and allowed some patients to enter part B before completing part A. Consequently, only the inter-episode analysis of the data could be performed.

2.3. Treatment

The treatment procedure consisted of pressing the lesion firmly for 1 min with a cotton wool pad immersed in freshly made solution prepared by dissolving a trial drug tablet in 3 ml of tap water. The procedure was repeated once with a new cotton wool pad. A new tablet was dissolved after 30 min, and again after a further 30 min, and the two-phase procedure repeated. The 3-tablet treatment course was carried out only once for each episode. One active drug tablet contained 100 mg ascorbic acid, 70 mg sodium percarbonate, 0.2 mg cupric sulphate, and necessary additives to make a tablet. The placebo had a similar appearance and the same constituents excluding ascorbic acid.

2.4. Follow-up

The presence and intensity of the following parameters were recorded by the patient before the treatment and, in principle, daily thereafter until complete healing. Unpleasant sensation, erythema, papules/vesicles, scab, and overall disturbance. All symptoms were graded mild/moderate/severe before the treatment and thereafter, a change in the intensity was recorded by ticking a box for increase/no change/decrease/disappearance. The nurse recorded erythema, swelling, papules, vesicles, ulceration, and scab. The nurse measured the diameters (d_{max}; d_{min}) of the lesion with a mm ruler and graded the intensity of the symptoms as mild/moderate/severe. The area of the lesion was calculated according to a formula ($d_{max} \times d_{min} \times 3/4$).

2.5. Virology

The nurse took a specimen for virus culture, trying not to damage the lesion mechanically, with a cotton wool-tipped stick, premoistened in Hanks' balanced salt solution, that was sent immediately to the virus laboratory. The specimens were inoculated during the same day into stationary tube cultures of continuous monkey kidney cell lines (GMK and Vero). Growth of herpes simplex virus was confirmed by immunofluorescence staining using type-specific monoclonal antibodies (Syva Co., Seattle, Washington).

2.6. Statistics

χ^2-test with the Mantel–Haenszel correction and the Fischer exact test were used to assess the significance of differences in class distributions and the Kruskall–Wallis test to compare linear or graded parameters between the two treatment groups.

3. Results

3.1. General observations

Forty-six volunteers (43 women and 3 men) with a median age of 43 years (range 21–64) were enrolled in the study. The median reported length of an episode was 7 days. In two-thirds of the patients, the episodes were always preceded by some kind of prodromal symptoms. The most usual lesion location was the lip, and in about two-thirds of the patients, the episode presented as multiple vesicles; 80% of the patients had tried some medication against the disease. The study population appears rather typical of herpes labialis (Spruance et al., 1977).

Patient and/or nurse records from 32 episodes were available for analysis, 14 of them had been treated with the active drug and 18 with placebo. Four episodes in the active group and 5 in the placebo group were patient-initiated. The two treatment groups did not differ significantly from each other at the time of treatment by any of the recorded parameters. Twelve out of 14 episodes in the active treatment group, and 17 out of 18 in the placebo group, had already reached the papulovesicular stage before treatment, with median duration times of 3 h 20 min and 3 h 40 min, respectively.

No major disagreement was found between corresponding records of the patient and the nurse. In a couple of cases a week-end or some other reason had stopped the recordings of the nurse before those of the patient, which may have caused some shortening of the apparent persistence of the nurse-recording symptoms.

Fifty percent of active drug-treated and 40% of placebo-treated patients complained of a short-term irritating sensation due to the treatment. No other side effects were reported or observed.

3.2. Patient data

The cumulative number of days recorded with symptoms after treatment was significantly smaller in the active treatment group than in the placebo group ($P < 0.02$). The number of patients with no erythema recorded after the treatment day was significantly greater in the active treatment group ($P < 0.05$). Likewise, the number of patients with no scab development or scab healing before day 3 was significantly larger in the active treatment group ($P < 0.05$) and the cumulative number of days with a scab was significantly smaller ($P < 0.01$) in the active group.

There was a general trend in most of the recorded parameters to have a shorter mean length of persistence in the active treatment group than in the placebo group (Table 1), but the two groups did not differ significantly from each other when assessed for mean

Table 1
Range and median duration of individual symptoms (days) in episodes treated with active drug or placebo

Symptom	Duration (days)				Statistical significance of difference
	Active drug		Placebo		
	Range	Mean	Range	Mean	
Patient recordings					
Unpleasant sensation	0–6	2.8	0–9	3.2	NS
Erythema	0–7	3.0	1–7	3.8	NS
Papules/vesicles	0–5	2.1	0–6	2.4	NS
Scab	0–8	3.8	0–13	5.8	NS ($P = 0.10$)
General disturbance	0–8	3.8	0–10	4.3	NS
Any symptom	0–8	4.5	1–13	6.1	NS ($P = 0.09$)
Nurse recordings					
Erythema	0–7	3.0	1–7	3.6	NS
Swelling	1–7	2.6	0–7	2.8	NS
Papules	0–4	0.4	0–1	0.1	NS [a]
Vesicles	0–4	1.5	0–4	1.4	NS
Ulcerations	0–6	1.1	0–3	0.5	NS [b]
Scab	0–8	3.4	3–9	5.9	$P = 0.03$
Any symptom	1–8	4.6	3–9	5.9	NS

Note that 'duration' means number of full days after treatment with the symptom recorded; NS, not significant;
[a] Only two positive recordings in both groups.
[b] based on 4 and 3 positive recordings, respectively.

duration, maximal intensity or for an increase in intensity of any given recorded symptom following the treatment. However, if the groups were compared for increase of the severity of any symptom after the treatment, this occurred significantly more often in the placebo group ($P < 0.05$).

3.3. Nurse data

The nurse-recorded length of the persistence of scabs was significantly shorter in the active treatment group than in the placebo group (3.4 vs 5.9 days, $P = 0.03$) (Fig. 1). Likewise, the proportion of daily records with a scab observed was significantly smaller in the active treatment group ($P < 0.01$) and the measured area of the scab was significantly smaller on days 6 and 7 after the treatment in the active treatment group ($P < 0.05$). In addition, like in the case of patient-recorded symptoms, there was a trend in some of the nurse-recorded parameters to have a shorter duration in the active drug-treated episodes (Table 1). The measured area of erythema also showed a trend to decrease more rapidly in the active treatment group of episodes (not shown). Papules and ulcerations were recorded so infrequently in the nurse follow-up that the numbers are not meaningful.

3.4. Virological data

About 80% of the specimens taken before treatment yielded herpes simplex virus in cell culture indicating that the patients were true herpes patients and that the sampling and culturing procedures were adequate.

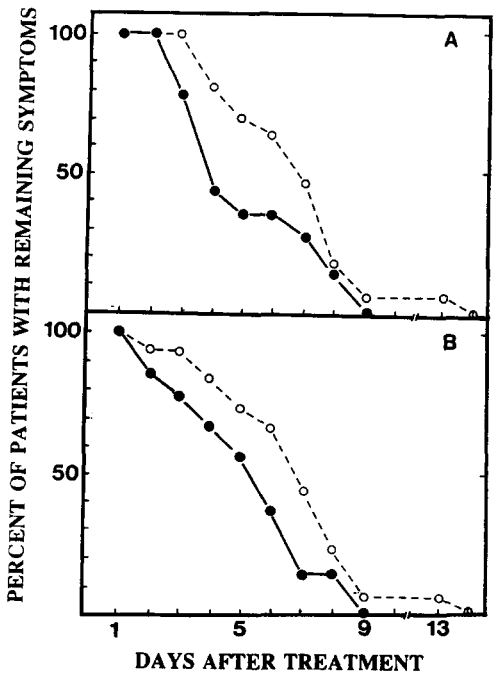

Fig. 1. Percentage of patients with any persisting symptom as recorded by the nurse (A) or the patient (B). ○, placebo; ●, active treatment.

During the second and the third day after treatment, specimens collected from the active treatment episodes yielded virus significantly less frequently than specimens from the placebo group ($P < 0.01$) (Fig. 2).

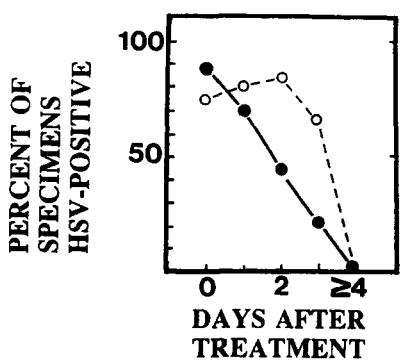

Fig. 2. Percentage of specimens yielding herpes simplex virus. ○, placebo; ●, active treatment.

4. Discussion

Antiviral chemotherapy has had remarkable success in recent years. Acyclovir has dramatically changed the course of serious disease caused by herpes simplex or varicella zoster (Saral et al., 1981; Strauss et al., 1984). A large number of other compounds have shown specific antiviral action (De Clercq, 1993) and some, such as foscarnet, have also shown potential for clinical use in genital herpes (Wallin et al., 1985). However, the most frequently encountered disease due to HSV, recurrent labial or non-genital mucocutaneous herpes, has remained an elusive target of antiviral treatment. The efficacy of topical or oral acyclovir has been frequently questioned, although it seems that at least the oral use is beneficial to some of the patients (Spruance et al., 1990; Higgins et al., 1993).

HSV can be isolated from recurrent labial or facial lesion usually only during a few days after onset of symptoms (Spruance et al., 1977). An antiviral treatment should, therefore, start very early in order to have a theoretical possibility of affecting the course of the disease. This may be difficult in doctor/nurse-initiated schedules in out-patients trials. On the other hand, patient-initiated schedules lack controlled assessment of the pretreatment status, which may be considered a confusing factor. We enrolled patients to this trial from the staff of the two institutes in order to guarantee rapid access to the study nurse. Even so, in several cases, the onset of an episode was during a week-end or other free time, making it impossible to reach the nurse within the required 24 h. Not unexpectedly, a large part of the enrolled patients who originally stated that they had recurrent herpes twice a year, never presented with herpetic lesion at the clinic during the trial. As a result, the number of evaluable episodes in the trial remained rather small.

Statistically significant differences between groups treated with the active drug and placebo were documented in some of the followed parameters according to both the patients' and the nurse's recordings, as well as by virus culture. The difference was most significant in the persistence of the scab and that of any symptom (time to complete healing), while a trend towards efficacy was seen in several of the registered symptoms. This general trend might be interpreted that the lack of statistical significance in the differences assessed for individual symptoms is most likely due to the small number of compared episodes. The failure to demonstrate a significant effect on duration of the vesicular stage was not surprising as most of the episodes had unfortunately already entered this stage before treatment. Larger studies with more strictly controlled timing of treatment are necessary to evaluate the true clinical significance of the observed small differences.

The mechanism of action of the treatment with Ascoxal solution is not known. Fresh Ascoxal solution appears to have a virucidal effect on HSV (T. Hovi, unpublished), but whether this could be the basis for the in vivo antiviral effect of topical treatment is not known. In addition to the observed antiviral effect, the procedure might directly affect the inflammatory reaction in the lesion. Percarbonate in the water solution is known to oxidize ascorbic acid, and it was originally suggested that the short-lived oxidization products of ascorbic are the antimicrobial effector molecules in Ascoxal solutions (Wahlqvist, 1958).

As is obvious from the minimal mode of treatment used in the trial, we expected, on

the basis of subjective experience, even more dramatic efficacy of the active preparation. On the other hand, we also wanted to be cautious, as the strength of the drug solution used in the trial was higher than that traditionally prescribed for oral antiseptic use. No significant side effects were observed. It is worth noting that the mean duration of disease in the placebo group was also clearly shorter than that reported in previous studies (Spruance et al., 1977), and slightly shorter than anamnestically reported by the present patient for previous episodes. This may simply be due to chance because of the small sample size.

In conclusion, we have shown that a brief topical treatment of mucocutaneous herpes with a percarbonate- and ascorbic acid-containing water solution may reduce the overall persistence of symptoms and ameliorate the symptoms during their persistence. The effect may have been more dramatic if the treatment procedure had been repeated several times.

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