Long-term suppression of severe recurrent genital herpes simplex infections with oral acyclovir: a dose-titration study

S Kroon, C S Petersen, L P Andersen, J Rønne Rasmussen, B F Vestergaard

Abstract

Twenty immunocompetent patients, four females and 16 males, with severe recurrent genital herpes (median number of recurrences the previous year 16, range (8-24)) entered an open continuous long-term suppressive treatment with oral acyclovir (ACV) for 12 months. The study included a dose-titration schedule: (ACV, 200 mg $\times$ 4/1-3 months, ACV, 400 mg $\times$ 2/4-6 months, ACV, 200 mg $\times$ 2/7-9 months, and ACV, 400 mg $\times$ 1/10-12 months). Patients with recurrences on steps two and three received an alternative dose of ACV, 200 mg $\times$ 3. Otherwise patients entered the previous dose-step. Five (20%) of patients were completely free of symptoms (recurrences and abortive lesions) during the four dose-reduction periods. A further nine patients (50%) could be dose-reduced to 200 mg $\times$ 3 without symptoms. Isolates from three patients showed a decrease in virus sensitivity after ceasing treatment. In conclusion, 14/20 of treated patients could be dose reduced to 200 mg $\times$ 2-3 without selection of HSV strains showing clinically important decreases in sensitivity towards ACV.

Genital infection with *Herpes simplex* virus (HSV) is an increasingly common problem, particularly in sexually active young adults and adolescents.^{1,2} In view of the AIDS epidemic, control and treatment of genital ulcerations has the utmost importance.³

Oral acyclovir has been shown to decrease significantly the duration and severity of genital herpes.⁴ Patients with frequent recurrent attacks

have been given oral acyclovir over 3 to 24 months to study the suppressive efficacy and safety of the drug.⁵⁻¹⁴ The acyclovir doses used in these studies were 200 mg three,⁷ four^{5,8-10} and five⁶ times daily. However, in one study⁶ an additional group of patients received 200 mg twice daily for 120 days, at which dose 65% of the patients had no recurrent lesions. In other studies where patients received 400 mg twice daily for 3, 12 and 24 months respectively, 71%,¹¹ 44%¹² and 29%¹³ of the patients were asymptomatic during the whole treatment period. In a study where patients received one daily dose of 800 mg acyclovir for 24 months, 28% of the patients remained free of recurrences.¹⁴ Because of the high cost of continuous treatment patients need advice concerning the optimum effective dose regime.¹⁵ Patients with very frequent attacks (> 8 per year) will often need the antiviral treatment for longer periods than 1 or 2 years to cope with a normal family, social and sexual life. This may increase the emergence of virus strains with decreased sensitivity towards acyclovir.^{16,17}

The aims of this study were to determine an optimum effective dose regime in patients, who were given continuous oral acyclovir for 12 months, and to assess viral sensitivity before, during and after treatment in patients, who normally suffer from very frequent recurrent attacks of herpes genitalis.

Methods

STUDY POPULATION

Patients with culture-confirmed genital herpes, who reported more than eight recurrences the previous year, were eligible to the study. Patients were enrolled between January 1986 and November 1986. Patients under 18 years of age, immuno-suppressed patients and patients who received any other specific antiviral therapy during or eight weeks before the study period were excluded. Women, who were pregnant or using inadequate contraception were not eligible. Approval was secured from the local ethical committee and the National Board of Health.

Department of Dermato-Venereology, Bispebjerg Hospital, University of Copenhagen
S Kroon, C S Petersen, J Rønne Rasmussen
Statens Seruminstitut, Copenhagen, Denmark
L P Andersen, B F Vestergaard

STUDY DESIGN

At the initial clinic visit, informed consent was obtained, a standardised medical history was taken, and a complete physical examination was conducted.

Whenever possible, treatment was initiated at the end of a recurrent episode. Patients received one tablet (200 mg) of acyclovir four times a day for three months. If no HSV lesions developed during this time, patients would take two 200 mg tablets of acyclovir twice a day for the next three months. Again, if no lesions developed, one 200 mg acyclovir tablet was taken twice a day for the next three months and two 200 mg tablets of acyclovir was taken once a day for the final three months of the study. If HSV lesions developed at any stage, patients were put back to the previous dosing regime. However, if lesions developed during the second or third three months period, patients received one 200 mg tablet three times daily, and only if lesions developed on this regime, patients would return to 200 mg four times daily.

PATIENT ASSESSMENT

During the whole study period patients were requested to complete a daily diary card of symptoms and to record the number of tablets taken. The patients attended the clinic at follow-up appointments every month and at the onset of any recurrences during treatment and the first two recurrences following the end of treatment.

Recurrences were divided into abortive and complete according to symptoms. Abortive lesions included prodromal symptoms, and/or local symptoms as redness, itching but without vesicles, ulcers or crusts. Complete recurrences were defined as eruptions including vesicles, ulcers and crusts. Swabs for virus isolation was taken prior to entering the study and during each recurrences and isolates were retained for acyclovir sensitivity testing. At entry and post treatment blood samples for haematology and biochemistry screening were taken.

VIRAL LABORATORY TESTING

Virus isolation and sensitivity testing

Clinical material was inoculated and transported in tubes with confluent human diploid fibroblast tissue to improve the isolation of HSV. The virus type was determined by ELISA.¹⁸ Isolates of HSV were propagated in two tissue cultures (human diploid fibroblast), one with and one without acyclovir. The concentration of acyclovir in the media was 0.5 µg/l × 2.2 µM. When full cytopathogenic effect had occurred in the tissue culture without acyclovir, both cultures were harvested and the amount of virus produced measured by double antibody sandwich ELISA (Andersen LP *et al.* In preparation). Inhibition was expressed as 100 minus the percentage of viral production in the presence of acyclovir com-

pared to the amount of virus produced without acyclovir. An inhibition of HSV of more than 80% indicates a full range of sensitivity, whereas an inhibition of less than 20% indicates HSV resistance to acyclovir.

Results

Twenty patients, 16 males and four females were enrolled in the study. Two male patients stopped before completing the whole study period. One patient left the study at month 10 because his job took him abroad. The other patient left the study at month 9, because of participation in another study involving potential immunomodulatory effects. Data from both patients are included in the study.

The median duration of recurrent herpes genitalis was 5 years (range 1–12), and the median number of attacks the previous year was 16 (range 8–24). Eight patients (40%) had herpes at two or more sites and 7 (37%) had extragenital herpes. Seven patients (37%) had tried other antiviral treatment, and eight (40%) had tried acyclovir systematically before. None had used acyclovir locally or systemically the previous 8 weeks.

Table 1 shows the number of patients with recurrences and abortive lesions in the four plus one treatment periods. One of twenty patients (5%) had recurrences in the first period, one of twenty (5%) in the second, six of nineteen (32%) in the third and two of eleven (18%) in the fourth 3 months period. Four (20%) of the patients had neither recurrent nor abortive lesions in the whole study period. In the first 3 months period 5 abortive lesions developed, the number decreased following continuous treatment, but rose to 36% in the low dose period (400 mg × 1) indicating break through lesions. None of the patients put back on 200 mg × 3 daily had recurrences or abortive lesions.

VIRUS ISOLATION AND SENSITIVITY TESTING

Table 2 shows inhibition of HSV in 18 patients treated with acyclovir. All virus typed was classified as HSV-2. Sensitivity testing of HSV isolates from 17 patients before treatment showed full sensitivity towards acyclovir. During treatment 15 virus isolation attempts turned out negative. Two virus isolate during treatment were positive for HSV, and both

Table 1 Number of patients with recurrences and abortive lesions during dose-titration with oral acyclovir

Month in the study	Dose of acyclovir	Number with recurrences (%)	Number with abortive lesions (%)
1–3	200 mg × 4	1/20 (5)	5/20 (25)
4–6	400 mg × 2*	1/20 (5)	1/20 (5)
7–9	200 mg × 2*	6/19 (32)	5/19 (26)
10–12	400 mg × 1	2/11 (18)	4/11 (36)
*	200 mg × 3	0/9 (0)	0/9 (0)

*Alternative dose if recurrences: 200 mg × 3.

Table 2 Inhibition assay of HSV Type 2 in 18 patients with severe recurrent genital herpes treated with oral acyclovir for 12 months

Pt no	Inhibition of HSV (%)		
	Before treatment	During treatment	After treatment
1	95	HSV × 1 pos: >97	87 >97
2	95	HSV × 1 neg	† 90 †
3	>95	HSV × 1 neg	80 >97
4	80	HSV × 1 neg	90 >97
5	HSV pos§	HSV × 2 neg	60 >97*
6	95	—	>97
7	90	—	93
8	90	HSV × 1 neg	93 >97
9	93	—	— 80
10	>97	—	neg neg
11	90	—	90 >97
12	>97	HSV × 1 neg	93 >97
13	>97	HSV × 2 neg,	—
		HSV × 1 pos: >97	>97 90
14	95	—	>97 >97
15	91	HSV × 1 neg	>97 >97
16	75	HSV × 5 neg	>97 60‡
17	>97	—	60
18	>97	—	>97

†No recurrences for two years following treatment.

§Sensitivity testing not available.

*Virus isolation performed from a new recurrent lesion 6 weeks apart from the first isolation.

‡The virus isolation was performed from a new lesion less than eight days apart from the first virus isolation.

strains showed full sensitivity towards acyclovir (>97%).

After treatment 23 isolates showed full sensitivity towards acyclovir (80%–>97%). Three virus isolates from three different patients after treatment showed decreased sensitivity (60%). One patient had an HSV-isolate 8 days earlier showing normal sensitivity (>97%), and the other patient had a normal HSV-isolate 6 weeks later showing full sensitivity (97%). The third patient had only one positive HSV isolate after treatment.

BLOOD TESTING

No changes in routine blood chemistry, haematological or liver function tests were seen after 12 months of treatment.

Discussion

This study of 12 months continuous treatment with oral acyclovir in decreasing and spaced doses in patients with very frequent genital herpes showed that 20% of the patients were completely free of symptoms during the four dose reduction periods, and a further 50% could be dose reduced to 200 mg × 3 without symptoms. Less than 50% could be dose reduced to 200 mg × 2 or 400 mg × 1. Although numbers of patients in this study are small, a much higher proportion of patients (70%) could be kept free of symptoms on a smaller dose (200 mg × 2–3 daily) than in most of the studies previously reported.^{12–14} An important factor was the higher starting dose allowing for the more

cost-effective dose reduction.¹⁵ Spacing doses makes continuous treatment more patient acceptable and increases compliance.

After termination of the study 79% of the patients continued drug treatment on the acyclovir dose that kept them free of recurrences, 16% had a change in recurrence rate and received intermittent local or oral treatment, and one patient with more than 24 recurrences in each of the previous 3 years did not experience a recurrence in the 2 years following termination of the study.

This variation creates a need for regular assessments of recurrence rates, (that is, once a year or every second year), and adjustment of treatment modalities and doses directed towards the individual patient.

Concern on the emergence of viral strains with decreased sensitivity or resistance patterns towards acyclovir has in the past been closely associated with patients who were immuno-compromised.¹⁷ Clinical important viral resistance strains in AIDS patients treated with acyclovir have recently been described.¹⁹ We found normal viral sensitivity both before and after the 12 months study period in fifteen of eighteen tested patients. However, three patients had a decrease in virus sensitivity. As a growing number of herpes patients will be treated with long term suppressive oral acyclovir changes in viral sensitivity may become a problem even in the immunocompetent patients. This stresses the importance of monitoring viral sensitivity in all patients on long term suppressive treatment with acyclovir or other antiviral drugs.

Address correspondence to: S Kroon, MD, Department of Dermato-Venereology, Bispebjerg Hospital, Bispebjerg Bakke 23, DK 2400 Copenhagen NV, Denmark

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