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Topical acyclovir cream in the treatment of genital herpes.

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A double-blind placebo-controlled trial of topical acyclovir cream was conducted in the treatment of initial and recurrent genital herpes. For seven patients with initial episiodes of genital herpes treated with acyclovir, the duration of all symptoms and the time to healing were significantly reduced and new lesion formation was completely prevented in comparison with the 5 placebo recipients. Of the cases with early recurrent genital herpes, 32 episodes treated with acyclovir were compared with 37 episodes treated with placebo. Acyclovir cream was proved to significantly reduce new lesion formation but other parameters showed only a trend in favour of acyclovir. A few patients reported minor local adverse reactions. Topical acyclovir cream is well tolerated and effective in initial genital herpes but for recurrent genital herpes, only some beneficial effects were shown.

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ในการทดลองใช้เอซัยคลอเวียรครีมทาเพื่อรักษาเริมที่อวัยวะเพศด้วยวิธี Double-blind placebo-controlled กับผู้ป่วยชายที่เป็นเริมที่อวัยวะเพศชนิดเป็นครั้งแรก ผู้ป่วย 7 คน ได้รับยาจริง 5 คน ได้รับยาหลอก ผลปรากฏว่าผู้ป่วยที่ได้รับยาจริงมีอาการและอาการแสดงทั้งหมดหายเร็วกว่ากลุ่มที่ใช้ยาหลอกอย่างมีนัยสำคัญ นอกจากนั้นผู้ป่วยที่ได้รับยาจริงจะไม่มีแผลใหม่เกิดขึ้นเลย ขณะใช้ยา สำหรับผู้ป่วยที่เป็นเริมที่อวัยวะเพศชนิดกลับซ้ำ มีการทดลองใช้ยาจริง 32 ครั้ง เทียบกับยาหลอก 37 ครั้ง ผลปรากฏว่าใช้เอวัยคลอเวียรครีมสามารถลดการเกิดแผลใหม่อย่างมีนัยสำคัญ แต่อาการอื่น ๆ ไม่ปรากฏผลแตกต่างกันเด่นชัด แต่มีนัยสำคัญทางสถิติ ผลแทรกซ้อนเฉพาะที่ของยามีเล็กน้อยกับผู้ป่วย 7 ราย แต่ไม่มีผลต้องยุติการศึกษา โดยสรุปแล้วเอซัยคลอเวียรครีมใช้รักษาแผลเริมที่เป็นครั้งแรกที่อวัยวะเพศได้ดี แต่ชนิดเป็นกลับซ้ำไม่ได้ผลดีเด่นชัด

In recent decades, genital herpes has climbed from relative obscurity to a position of being one of the most common sexually transmitted diseases now seen.[1] It is primarily a disease of the young adult population.[2-5] Acyclovir, ("Zovirax", Wellcome) an antiviral with a unique virus-specific mechanism of action against Herpes simplex virus 1 (HSV 1) and HSV 2 is an excellent candidate for treatment of HSV infections. Topical acyclovir ointment has been shown to diminish the duration of virus shedding and local symptoms in the first episode of infection but to have little effect in recurrent genital HSV infections.[6] In an animal model for cutaneous infections acyclovir cream was superior to acyclovir ointment.[7] We report the results of a double-blind, placebo-controlled clinical trial of topical acyclovir cream in the treatment of initial and recurrent episodes of genital herpes.

PATIENTS AND METHODS

Male patients presenting with clinically diagnosed initial episodes and recurrent (or with a history of recurrent) genital herpes, at the Sexually Transmitted Diseases Clinic, Chulalongkorn Hospital, Bangkok, were invited to participate in the study.

Patients aged less than 15 years, treated with other specific antiviral therapy in the preceding 14 days or having other diseases that might interfere with the assessment, were excluded from the study. Patients with the first episode of genital herpes presenting within 5 days of onset of their lesion, were eligible for entry. Recurrent genital herpes patients presenting with lesions within 24 hours of onset were instructed on early self medication. Those with an onset of longer than 24 hours were given the same recomendation for any subsequent recurrence that is, immediately any prodrome began or when the first lesion appeared. Ethical committee approval of the study was obtained as was verbal consent from all the patients involved.

A history relating to herpes infection and other sexually transmitted diseases was taken as well as a full clinical examination. At presentation, laboratory tests including VDRL, two neutralizing antibody tests for herpes two weeks apart, Tzanck smear, antigen detection by fluorescent antibody technique (FA) and dark ground microscopy in some cases were also performed. For initial or recurrent episodes, patients were supplied with a 10 gram tube of 5% acyclovir cream in aqueous cream base or matching placebo containing the cream base alone on a double blind basis. They were instructed to apply the cream four times a day for up to ten days or until healing had occured. Clinical assessments were made two to three times a week until complete healing occured. Symptoms and signs were scored subjectively at each visit from 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe). Lesions were classified as erythema only, papules, vesicles/pustules, ulcers/erosions, crusts and healed. They were grouped as original lesions and new lesions.

Those patients with clinically diagnosed genital herpes either with or without a positive Tzanck smear were chosen to enter the study. For evaluation, only patients with clincal features of the disease, a positive Tzanck smear and/or FA and with neutralizing antibody presenting at the second or both of the two blood samples and who had complete follow-up were selected.

STATISTICAL ANALYSIS

Assessed parameters were analysed by using unpaired t-test, Fisher's exact probability test and non-parametric test.

RESULTS

From 12th March 1985 to 5th January 1987, a total of 97 patients from the sexually Transmitted Diseases Clinic, Chulalongkorn Hospital, presenting with the first (initial) or recurrent episodes of genital herpes were entered into the study. Fourteen patients with the first eqisode of genital herpes were studied. Five were in the placebo group and seven in the acyclovir group, but two failed to return to the clinic for the follow-up visits (1 acyclovir and 1 placebo) and so were excluded from the analysis of the results (Table 1). Acyclovir reduced the duration of crusting and healing of original lesions and the formation of new lesions. The result for pain and itching appeared less impressive because the numbers were small and the infections were less severe in those patients (Table 3)

Table 1. Groups of Patients Receiving Acyclovir or Placebo.

Group	Acyclovir	Placebo	P-value	Total Episode	Patient No	P-value
Initial:						
Complete Follow up	7	5	P = 0.6923*	12	12	P = 0.7022
Incomplete Follow up	1	1		2	2	
Recurrent :						
Complete Follow up						
Early	16	16		32	32	
Self-Medicated	11	14		25	25	
Secondary Episode	5	7		12	—	
Incomplete Follow up			P 0.0001*			P = 0.0001**
No return	12	10		22	22	
VDRL-reactive	2	2		4	4	

* Fisher's exact test
** Statistically significant.

Table 2. Details of Patient at presentation.

Details of Patient at Presentation	Initial			Recurrent		
	Acyclovir N = 7	Placebo N = 5	P-value	Acyclovir N = 27	Placebo N = 30	P-value
1. No. of Episode	7	5	—	32	37	—
2. Age	22.4	24.6	P 0.05**	23.6	26.3	P 0.05+
3. Duration of attack (days)	6.7	6.2	P 0.05**	5.3	5.7	P 0.5+
4. Previous Episodes Per year (Median)				3	4	P=0.07
5. Pain/Discomfort Score	2.4	2.5		1.3	1.5	P=0.07
6. Inguinal Lymph adenopathy(%)	71	60	P=0.102*	42	45	P=0.669
7. No. of Antibody Negative	4	3	P= 0.689*	—	—	—
8. No of infection in partner (%)	43	40	P=0.667*	22	29	P=0.256

* Fisher's exact test
** Unpaired t-test
+Statistically significant
*** Non-parametric test

Table 3. Result for Initial and recurrent Episodes of Genital herpes*.

Outcome	Initial			Recurrent		
	Acyclovir N = 7	Placebo N = 5	P-value	Acyclovir N = 27 Episode = 32	Placebo N = 30 Episode = 37	P-value
1. Duration of itching	3	7	P=0.0720	3	4	P=0.0892
2. Duration of pain	4	8	P=0.5581	2	3	P=0.011**
3. Duration of all symptoms	4	8	P=0.04455**	3	4	P=0.0002**
4. Time of healing	6	12	P=0.0101**	6	7	P=0.0148**
5. New lesion formation (%)	0	40	P<.0001**	6	24	P=0.0003**

* Results are given as median times in days
** Statistically significant

Of the 83 recurrent genital herpes patients enrolled in the study, only 57 returned and completed the treatment. The remaining 22 patients (12 acyclovir and 10 placebo) failed to return for follow-up assessments, or both blood samples were negative for neutralizing antibody. Another 4 patients had to be excluded from the study because they had positive VDRL reaction (2 acyclovir, 2 placebo). The 69 recurrent episodes studied consisted of 32 patients presenting with early lesions (16 acyclovir, 16 placebo). The remaining 25 patients (11 acyclovir, 14 placebo) were self-medicated, with 12 in this group having two epsodes (5 acyclovir, 7 placebo) (Table 1)

Time to complete healing of all lesioons, duration of new lesion formation, duration of pain and duration of all symptoms were reduced with statistical significance in the acyclovir group compared with those treated with placebo. The duration of itching showed a trend in favour acyclovir treated group but was not statistically signigicant. (Table 3)

ADVERSE REACTIONS

There was no significant differences between the number of patients developing adverse reaction in both groups with only minor reactions being noted (Table 4). No patient was withdrawn from the therapy because of an adverse event. The events occurred during the first episodes more frequently than in recurrent ones probably bacause of the more extensive lesions in the former geoup.

Table 4. Local Adverse Reaction.

Local adverse reaction	Acyclovir	Placebo	P-value Fisher's
Initial Episodes :	N = 7	N = 5	
Burning	1	1	P=0.682
Rash	0	0	—
Itching	1	0	P=0.716
Recurrent Episodes :	N = 27 Episode=32	N = 30 Episode=37	
Burning	1	1	P=0.716
Rash	0	0	—
Itching	1	1	P=0.716
Total No.of adverse reaction	4(10%)	3(7%)	P=0.447

DISCUSSION

Acyclovir has received a most extensive testing in herpes simplex infections, including initial and recurrent genital herpes. The topical acyclovir ointment formulation has been studied as therapy for the initial, or first episode of genital herpes.[6] Patients with both primary disease (no pre-existing HSV antibody) or non-primary (positive HSV antibody during the acute phase) were included in this study. The duration of pain, itching, and all symptoms combined were shorter in the treated than in the control group, but only the last was statistically significant because of the samll number of patients. Time to healing was recorded from onset of the first sign and all lesions in the acyclovir group were completely healed, within 4 days in comparision to 8 days in the placebo group. New lesion formation was completely prevented in the acyclovir group. Adverse reactions occurred during primary episodes more than in non-primary cases because of the extensive lesions. For various parameters, acyclovir was superior to placebo in initial genital herpes.

In recurrent genital herpes, topical acyclovir ointment has shown little demonstrable effect on lesion resolution or duration of symptoms, but has reduced the number of patients in whom new lesions developed (from 24% to 6%) which has been shown earlier.[6] This is most probably due to the shorter duration of recurrent genital herpes attacks. Patients should start the therapy within 24 hours of symptoms or during the prodromal period to maximize clinical benefit. In this study, as in others involving the aqueous cream formulation, the effect of topical acyclovir in recurrent genital herpes was apparent but was less pronounced than in the first episode.[8]

Acyclovir has not been shown to effect either viral latency or the recurrence of genital herpes. In animal studies it had no effect on the establisshment of ganglionic infections.[9] In this study there were 5 second recurrences in twelve of the self-medicated acyclovir group and 7 out of the fourteen placebo group.

We conclude that acyclovir cream appears to be a safe, well-tolerated, and effective preparation for the treatment of the initial attack of genital herpes, which can be managed effectively on an out-patient basis. For recurrent attacks, it had a less significant demonstrable effect on lesion resolution and duration of symptoms except for new lesion formation.

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