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Treatment of herpes genitalis with carbenoxolone and cicloxolone creams:

A double blind placebo controlled clinical trial

G W CSONKA* AND D A J TYRRELL†

*From the *Department of Genitourinary Medicine, St Mary's Hospital, London W2 and the †Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex*

SUMMARY Preliminary results in vitro have indicated that carbenoxolone and analogues possessed activity against herpes viruses. We undertook a double blind clinical study to compare the efficacy of carbenoxolone and cicloxolone creams with placebo in initial and recurrent herpes genitalis. Seventy-nine patients (21 of whom were entered in the trial more than once) received 105 courses of treatment, 83 of which were suitable for life table analysis. There were significant differences in the time to disappearance of pain ($p = 0 \cdot 044$) and the healing of lesions ($p = 0 \cdot 023$) in favour of cicloxolone compared with placebo. Carbenoxolone showed some beneficial effect compared with placebo, but this was not significant. Results on day 5 were similar. The only adverse reaction was mild erythema with irritation in one patient in each treatment group. We conclude that further trials with more extensive virological investigation are indicated to confirm the beneficial effect of cicloxolone.

Introduction

In an earlier study of balanitis, some cases of which were associated with herpes simplex, it was found that the topical application of carbenoxolone sodium gel (2%) gave promising results.[1] This compound was chosen because of its reported efficacy in healing ulcers and erosions of mucous membranes. It was later decided to try topical carbenoxolone and the chemically related cicloxolone in an open study of patients with confirmed herpes genitalis. The results showed that the preparations speeded healing both in initial and recurrent attacks. As herpes genitalis has a notoriously unpredictable course and the placebo effect can be as high as 60%, we undertook a double blind placebo controlled trial.

LABORATORY ANTIVIRAL STUDY

In a preliminary study, carbenoxolene and some close analogues were tested for antiviral effects in tissue culture. The drugs were administered in the presence of albumin and diluted with maintenance medium. The drugs were tested in cultures of Hela cells or human fibroblasts (MRC 5) which were challenged with about 1000 median tissue culture dose of recently isolated herpes simplex viruses and observed for three days. The drugs, which were at high concentrations, appeared to be rather toxic and caused the cells to 'round up' in the absence of virus. With some analogues at sub-toxic concentrations, however, the viral effect was delayed or prevented. An antiviral effect was seen with carbenoxolone 10^{-4} mol/l against an oral strain, and $10^{-3 \cdot 5}$ mol/l against a genital strain. Other analogues of carbenoxolone were also active against the oral strain. By ordinary criteria, however, these substances would have been regarded as too toxic in vitro, even when protein bound, to warrant further testing. As carbenoxolone is not toxic for epithelial cells in vivo, it was thought reasonable to try to confirm the open clinical effect by a double blind trial, and to bear in mind that in clinical use any beneficial effects seen might be due to inhibition of virus replication.

Patients and methods

Patients of either sex who had herpes genitalis and attended the Praed Street Clinic of St Mary's Hospital, London were invited to enter the study

Address for reprints: Dr G W Csonka, John Hunter Clinic, St Stephen's Hospital, Fulham Road, Chelsea, London SW10 9TH

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provided they gave informed consent, presented within 48 hours of the onset of a recurrent attack or within five days of an initial attack, were over 16 years of age, had no other clinically obvious genital infection, and had not received antiviral treatment within the previous 14 days. Of patients with initial attacks of herpes genitalis—that is, with no history of previous attacks and in whom the episode lasted two to four weeks (probable primary infection)—only those with a positive culture for herpes simplex virus (HSV) were included in the subsequent analysis. Patients with recurrent herpes genitalis who had previously had a positive HSV culture were analysed whether the present culture was positive or not. Other sexually transmitted diseases were ruled out by the appropriate tests.

We intended to take samples for culture every other day until the lesions were healed. Data on the type, site, and extent of lesions and the presence or absence of prodromal symptoms were noted, as were the date of onset of symptoms, the date when the cream was first applied, the times to the disappearance of itching and of pain, and the times to crusting and complete healing. The severity of symptoms and lesions were assessed at each visit on a four point scale (for lesions: 1 = severe, 2 = moderate, 3 = mild, 4 = absent; for symptoms: 1 = worse, 2 = same, 3 = mild, 4 = absent). Side effects were enquired into and recorded. After the lesions had healed the patients were asked for their assessment of the treatment.

The medicated cream contained either 2% carbenoxolone sodium or 2% cicloxolone sodium; the control cream was of the same formula but contained neither test medication (Biorex Laboratories Limited). The creams were dispensed in numbered 15 g tubes. Patients were instructed to apply the preparation sparingly to the lesions five times a day for seven days, or for the the duration of the lesions and for 24 hours after healing, whichever was the shorter period. They were asked to attend on alternate days for the first four to six days, on day 7 and day 14 after the start of treatment, and at any time if the lesions did not heal or if new lesions developed during the period of the trial. Swabs were taken for confirmation of the presence of HSV at each attendance while the lesions were present.

Of the 79 patients entered into the study, 21 were entered again with further attacks (four of them were entered more than twice). They then received another randomised tube of cream. Each treatment period was counted as a separate and distinct "patient". Ten patients were excluded from the analysis due to late entry or inadequate viral confirmation, one patient was excluded because of misdiagnosis, and 11 patients defaulted, making a total of 22 exclusions. Patients in the three treatment groups showed a similar distribution as regards age, marital status, socioeconomic group, and frequency of past attacks of herpes genitalis.

Results

Table I shows that the number of patients with initial or recurrent herpes genitalis in each of the three treatment groups was similar. Of the 19 patients with initial attacks of herpes genitalis, 11 could be fully analysed. Some patients had more than one attack during the six month study period and of the 86 recurrent episodes, 56 had a positive viral culture on entry and 83 were analysed.

Table II shows the results at the end of the study. The mean score for severity of lesions before treatment in all patients with recurrent attacks was 2·18 in the carbenoxolone group, 2·17 in the cicloxolone group, and 1·93 in the placebo group.

TABLE II *Results at the end of the study.*

Results at end of study	*Carbenoxolone (n = 29)*	*Cicloxolone (n = 32)*	*Placebo (n = 33)*
Patients with healed lesions	22	31	20
Patients with no pain	21	30	21
Patients reported healed and free of symptoms (but not seen) included above	2	2	NIL
Defaulters (on days 1 and 2) included above	3	1	7

n = total number of patients complying with protocol including defaulters.

TABLE I *Numbers of patients with initial or recurrent episodes in the three treatment groups*

	Initial herpes genitalis			*Recurrent herpes genitalis*		
	Carbenoxolone (n = 6)	*Cicloxolone (n = 7)*	*Placebo (n = 6)*	*Carbenoxolone (n = 29)*	*Cicloxolone (n = 28)*	*Placebo (n = 29)*
Men	3	4	2	21	19	23
Women	3	3	4	8	9	6
Defaulters	0	0	0	3	1	7
Exclusions	4	2	2	2	1	0
Acceptable for analysis	2	5	4	24	26	22

n = total number of patients entered.

All the patients with initial attacks of herpes genitalis had a lesion severity score of 1 before treatment, with the exception of one in the cicloxolone group who had a score of 2. Patients with unhealed lesions or with continuing symptoms on day 6 or later who then defaulted were classed as treatment failures. Patients whose lesions did not heal but became worse during the first seven days were transferred to an alternative treatment, and were classed as treatment failures. Patients whose lesions healed but who suffered a recurrence during the first seven days were classed as having been healed.

Life table analysis of the data from the 94 "patients" (initial episodes and recurrent attacks) showed that both carbenoxolone and cicloxolone were associated with faster healing and more speedy relief of pain than placebo; this difference for cicloxolone was significant ($p = 0{\cdot}0437$) for pain and ($p = 0{\cdot}0228$) for healing (figure).

In view of the significant results obtained in the life table analysis a further explanatory analysis was carried out. As the recurrent lesions could be expected to heal spontaneously by the tenth day in most patients, we decided to analyse the results obtained at five days before decoding the study. Patients who defaulted before day 5 were excluded from this analysis. Fisher's exact probability test was used to analyse the differences between carbenoxolone, cicloxolone, and placebo in (a) patients with recurrent herpes genitalis and (b) the combined group with initial and recurrent herpes genitalis, as the number of patients with an initial attack was too small for separate statistical analysis. Table III shows that, although carbenoxolone gave some benefit in the treatment of herpes genitalis this was not significant. Cicloxolone was significantly better than placebo in both the recurrent and the combined groups. Cicloxolone was also more effective than carbenoxolone. Thus comparison of cicloxolone with carbenoxolone in this relatively small group of patients showed a difference in favour of cicloxolone, although this was not significant at the conventional level.

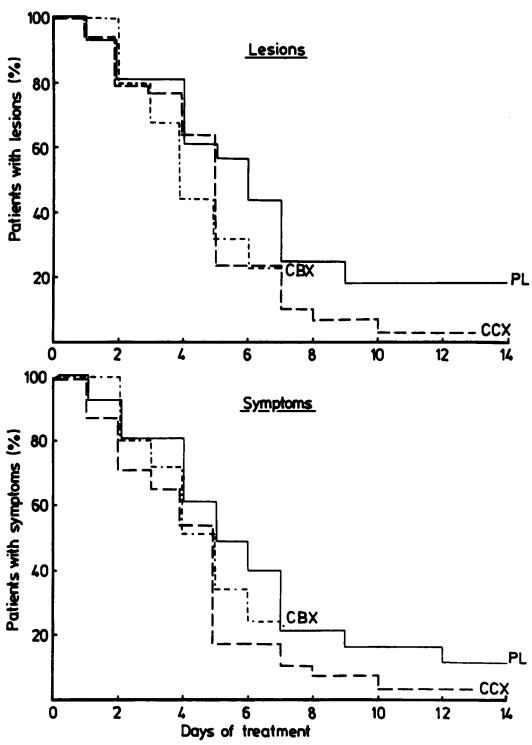

FIGURE *Reduction in lesions and symptoms in patients with herpes genitalis treated with carbenoxolone (CBX), cicloxolone (CCX), or placebo (PL). Defaulting patients and those not healed by day 14 (eight treated with carbenoxolone, two with cicloxolone and 13 with placebo) were included in the life table analyses.*

ASSESSMENT BY PATIENTS

About three quarters of the patients with recurrent attacks who had experience with other treatments, including topical acyclovir, thought that the test preparations gave a more rapid relief from discomfort.

PATIENTS ENTERED MORE THAN ONCE INTO THE STUDY

Of the 29 patients who returned with recurrent lesions, 22 were entered again. As the study continued to be double blind, the repeat treatment was random. The numbers are too small for formal analysis, but it appeared that drug treatment was equally effective on subsequent occasions.

SIDE EFFECTS

Only three patients, one in each of the three groups, had slight erythema and irritation after applying the cream, but this was not severe enough to interrupt treatment. No other adverse reactions were observed.

Discussion

An open study of 11 cases with herpes labialis in 1971 showed a beneficial effect of carbenoxolone gel.[2] In another open study 12 patients with acute herpetic stomatitis due to HSV 1 were treated with carbenoxolone mouthwash with promising results.[3] The possibility of a link between herpes virus infection and duodenal ulceration has been discussed, and mention made that glycyrrhizic acid, the precursor of carbenoxolone, possessed antiviral properties.[4] For these reasons and those given in the

TABLE III *No (%) of patients with initial and recurrent herpes genitalis who were healed at day 5 and at end of treatment*

	Recurrent herpes genitalis			*Initial herpes genitalis*			*Significance†*	
Status of healing and pain	*Carbenoxolone (n = 24)*	*Cicloxolone (n = 26)*	*Placebo (n = 22)*	*Carbenoxolone (n = 2)*	*Cicloxolone (n = 5)*	*Placebo (n = 4)*	*Carbenoxolone*	*Cicloxolone*
Free of lesions at 5 days	16 (67)	22 (85)	11 (50)	1 (50)	2 (40)	0 (0)	p = 0·164	p = 0·014
Free of lesions at end of treatment	20 (83)	26 (100)	18 (82)	2 (100)	5 (100)	2 (50)	p = 0·726	p = 0·013
Free of symptoms at 5 days	15* (62)	22* (85)	12 (55)	1 (50)	3 (60)	1 (25)	p = 0·577	p = 0·030
Free of symptoms at end of treatment	19* (79)	25* (96)	19 (86)	2 (100)	5 (100)	2 (50)	p = 0·999	p = 0·125

n = total number of patients acceptable for analysis; percentage of those patients who were healed is given in parentheses.
*One patient defaulted when free of lesions but with mild symptoms.
†Combined results from patients with initial and recurrent attacks. Differences between carbenoxolone or cicloxolone and placebo using Fisher's exact probability test (two tail).

introduction we designed this comparative study. Life table analysis showed a significant difference in favour of cicloxolone compared with placebo in the time to disappearance of discomfort and the healing of lesions. Carbenoxolone appeared to be somewhat less effective. The relief of pain and discomfort was spontaneously remarked upon by many patients in this study as well as in our earlier experience. This effect is possibly non-specific in the sense that it is not the result of direct action of the drug on the virus. For this reason the results of the antiviral investigations in animals and further studies in vitro, which are now in progress in several laboratories, are awaited with interest. It will also be essential to mount a larger clinical study, with more complete data on virus shedding, and to include virus typing to confirm the present findings. The next step will therefore be to compare the more effective of the two preparations with acyclovir cream, even though this may have to be a single blind trial.

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