with other illnesses necessitating intensive monitoring of numerical data,[9] and to the evaluation of series of data collected in the course of research.

We thank Professor Roger Blamey, Dr Richard Burden, and the many other colleagues who helped in the care of these patients and in their investigations. The study was supported by grants from the Medical Research Council and the Nottingham and Nottinghamshire Kidney Fund.

References

1 Cosimi AB, Colvin RB, Burton RC, *et al.* Monoclonal antibodies for immunological monitoring and treatment in recipients of renal allografts. *N Engl J Med* 1981;**305**:308-14.
2 Foegh ML, Winchester JF, Zmudha, *et al.* Urine i-TXB_2 in renal allograft rejection. *Lancet* 1981;ii:431-4.
3 Knapp MS, Cove-Smith JR, Dugdale R, Mackenzie N, Pownall R. Possible effect of time on renal allograft rejection. *Br Med J* 1979;i:75-7.
4 Harrison PJ, Stevens C. Bayesian forecasting. *Journal of the Royal Statistical Society. Series B.* 1976;**38**:205-47.
5 Freedman AM, Duneman OP, Peckham G, Trattner A. Automatic recognition of significant events in the vital signs of neonatal infants. *Comput Biomed Res* 1978;**12**:141-8.
6 Wilson DW, Griffiths K, Kemp KW, Nix ABJ, Rowlands RJ. Internal quality control of radioimmunoassays: monitoring of error. *J Endocrinol* 1979;**80**:365-72.
7 Chik L, Sokol RJ, Rosen MG, Pillay SK, Jarrell SE. Trend analysis of intrapartum monitoring data: a basis for a computerised fetal monitor. *Clin Obstet Gynaecol* 1979;**22**:665-79.
8 Royston JP, Abrams RM. An objective method for detecting the shift in basal body temperature in women. *Biometrics* 1980;**36**:217-24.
9 Stoodley KDC, Mirnia M. The automatic detection of transients, step changes and slope changes in the monitoring of medical series. *Statistician* 1979;**28**:163-70.
10 West M, Smith AFM. Monitoring renal transplants: an application of the multi-process Kalman Filter. *Biometrics* (in press).
11 Knapp MS, Blamey RW, Cove-Smith JR, Heath M. Monitoring the function of renal transplants. *Lancet* 1977;ii:1183.
12 Van der Helm HJ, Hische EAH. Application of Bayes's theorem to results of quantitative clinical chemical determinations. *Clin Chem* 1979;**25**:985-8.
13 Knapp MS, Smith AFM, Trimble I, Pownall R, Gordon K. Mathematical and statistical aids for evaluating sequences of data collected from renal patients. *Kidney Int* (in press).
14 Jelliffe RW, Jelliffe SM. A computer program for estimation of creatinine clearance from unstable creatinine levels, age, sex and weight. *Mathematical Biosciences* 1972;**14**:17-24.
15 Mitch WE, Walser M, Buffington GA, Lemann J. A simple method of estimating progression of chronic renal failure. *Lancet* 1976;ii:1326-8.
16 Rutherford WE, Blondin J, Miller JP, Greennalt AS, Vavra JD. Chronic progressive renal disease: rate of change of serum creatinine concentration. *Kidney Int* 1977;**11**:62-70.
17 Gordon M, de Wardener HE, Venn JC, Webb JT, Adams H. The interactive graphic database microcomputer for clinical use in data intensive therapies. *Proc Eur Dial Transplant Assoc* 1981;**18**:690.
18 Anonymous. Kidneys and computers [Editorial]. *Br Med J* 1980;**281**:1302-3.

(*Accepted 17 December 1982*)

Successful treatment of herpes labialis with topical acyclovir

A PAUL FIDDIAN, JANE M YEO, RONALD STUBBINGS, DONALD DEAN

Abstract

A double blind, placebo controlled trial of 5% acyclovir cream, applied topically five times a day for five days, was carried out in 49 patients with recurrent herpes labialis. These patients had a total of 74 episodes, 34 of which were treated with the 5% acyclovir cream and 40 with matching placebo. First episodes and all episodes treated with acyclovir cream had significantly shorter times to formation of ulcer or crust and to complete healing ($p<0.05$ for all variables). The duration of all symptoms and proportion of patients developing itching was also reduced by acyclovir cream in first episodes, though the difference was not significant. When the patient started treatment early in the course of a first episode acyclovir cream significantly reduced the percentage of lesions progressing beyond the papular stage ($p<0.05$).

Acyclovir cream is well tolerated and effective for the treatment of recurrent herpes labialis.

Department of Clinical Immunology and Chemotherapy, Wellcome Research Laboratories, Beckenham, Kent BR3 3BS
A PAUL FIDDIAN, MB, research physician
JANE M YEO, PHD, clinical research assistant

Medical Services, British Petroleum Company Limited, Britannic House, London
RONALD STUBBINGS, MB, medical officer
DONALD DEAN, MB, head of medical services

Correspondence and requests for reprints to: Dr A Paul Fiddian.

Introduction

Recurrent herpes simplex infections around the mouth (herpes labialis, cold sores, fever blisters) occur in up to one fifth of young adults,[1 2] but no treatment has hitherto been shown in double blind, placebo controlled trials to have an appreciable clinical benefit. The discovery of acyclovir (Zovirax, Wellcome), an antiviral drug with highly specific activity against herpes simplex virus types 1 and 2,[3] offers the possibility of a safe and effective topical preparation for the treatment of recurrent herpes simplex virus infections. Oral acyclovir has been shown to be effective in the treatment of recurrent genital herpes,[4] and topical acyclovir in an ointment base (polyethylene glycol) shortens the duration of virus shedding in patients with recurrent genital herpes[5] and herpes labialis,[6] without producing a demonstrable clinical benefit. The limited effect of local antiviral treatment in recurrent herpes simplex virus infections may be due to poor skin penetration of the drug, and on this account it has been suggested that acyclovir be applied using dimethyl sulphoxide as the vehicle.[6 7] An alternative formulation using propylene glycol as solvent has been found to be superior to acyclovir ointment for the treatment of experimental cutaneous herpes simplex virus infections in animals.[8]

It has been suggested that recurrent herpes labialis will complete its natural course unless specific antiviral treatment with acyclovir is initiated early, before the lesions become established.[6] To achieve this, patients need to be supplied beforehand with the acyclovir cream, which should be applied at the onset of prodromal symptoms or signs. Studies of the clinical course and treatment of herpes labialis at the Wellcome Research Laboratories indicated that only about 2% of an otherwise healthy population experienced recurrent herpes labialis frequently or severely enough to volunteer for placebo controlled trials.[9] To obtain a pool of volunteers known to suffer from recurrent herpes labialis, we approached about 5000 employees at the headquarters of the British Petroleum Company in London. We report the results of a randomised, double blind trial of acyclovir cream in subjects with a history of recurrent herpes labialis who attended the medical centre of the British Petroleum headquarters.

Patients and Methods

A brief questionnaire was sent to about 4500 employees at Britannic House. We selected 90 patients who gave a history of at least two recurrences of herpes labialis per year and were prepared to volunteer for inclusion in a controlled trial. Those aged under 18 years were excluded. Informed consent was obtained from all patients and permission to include their patients was sought from their general practitioners. As a result, 87 patients were randomly allocated under double blind conditions to receive a 10 g tube of 5% acyclovir cream or matching placebo. Patients were instructed to begin applications of the cream as soon as possible after the onset of the first prodromal symptoms of their next attack. Treatment was to be continued five times a day for five days. Patients were to attend the clinic where possible within 24 hours of beginning treatment and to return daily until healing occurred, unless a weekend or public holiday intervened.

A detailed history and clinical assessments were recorded at each visit. Lesions were classified as erythema, papule, vesicle, ulcer or crust, loss of crust but not yet healed, and completely healed; the size and site of the lesion was also noted. Symptoms were recorded as itching, pain or burning, or other, and any possible adverse effects were identified. In addition, the patient was required to keep a record of the exact time of onset and nature of their first symptoms and signs and the time applications were commenced. An attempt to assess compliance was made by asking the patient to note each application during the course of treatment. Subjective assessments of efficacy were also noted by the patient. Virological and laboratory safety tests were not practicable but were felt to be unnecessary considering what was already known about the drug.

After each treated episode patients were rerandomised to acyclovir or placebo for their next episode. Only patients with frequent recurrences tended to be included for further episodes. The low recurrence rate in many patients meant that a formal crossover trial design was impractical. In any case, such a study method was thought to have potential problems if any carryover effect was present. It is recognised that the data from subsequent episodes should be interpreted with caution, but the results are included for additional information.

The data were entered into a computer using the Clindata system,[10] and a dual entry system was used to control errors. The treatment groups were compared for various variables in history and initial assessment (table I) using a Mann-Whitney U test or χ^2 test. The data on efficacy were analysed using the log rank test for all the variables given in table II, apart from the comparison of proportions, for which Fisher's exact test was used.

TABLE I—*Details of patients at presentation*

	Placebo (n = 25)	Acyclovir (n = 24)
No of men*	15	15
No of women*	10	9
Age (years)†	35	37
Age at onset of disease (years)†	15	15
No of recurrences per year†	3	3
Frequency of prodrome‡	Usual	Usual
Average lesion:		
No†	1	1
Size (mm)†	5	5
Duration (days)†	8	8
Time since last recurrence (months)†	2	3·5
Time to first application (hours)†	1	4
Lesion stage at first application‡	Papule	Papule

* Compared using a χ^2 test (remainder compared using a Mann-Whitney U test).
† Median values.
‡ Parameters were converted to numerical scores for statistical analysis and then median values were changed back to descriptive terms.

Results

Although 87 patients were entered into the study only 55 fulfilled criteria for inclusion—namely, had documented recurrences during the study period, started treatment within 24 hours of onset of the attack, and attended the clinic for assessments. Of these, a further six were excluded, four because they attended too infrequently and two because of concomitant use of other medications, leaving 49 patients evaluable for analysis. Table I gives the details recorded during the initial interview and clinical assessment of the 49 patients. No statistical differences in these variables were found between the patients treated initially with acyclovir or placebo. Some of the patients with more frequent recurrences were then rerandomised to treatment so that a total of 74 episodes were included in the overall analysis of efficacy. Greater weight should, however, be given to the analysis of first episodes only.

The percentage of lesions in first episodes that aborted—that is, failed to progress beyond the papule stage—was significantly greater in patients treated with acyclovir whether all of them or only those treated before vesicles had developed were included (table II). For all episodes there were trends in favour of acyclovir but these did not reach significance. Two types of abortive lesions were noted; those that never progressed beyond the erythema stage were termed completely abortive and those that developed papules but not vesicles were termed partially abortive. As erythema alone was not considered as a stage of lesion, completely abortive lesions were recorded as healing on day 0. There were four such lesions in the acyclovir group compared with none in the placebo group and this explains why the acyclovir curves in the figure start at less than 100%. For first episodes treated with acyclovir there were four partially abortive

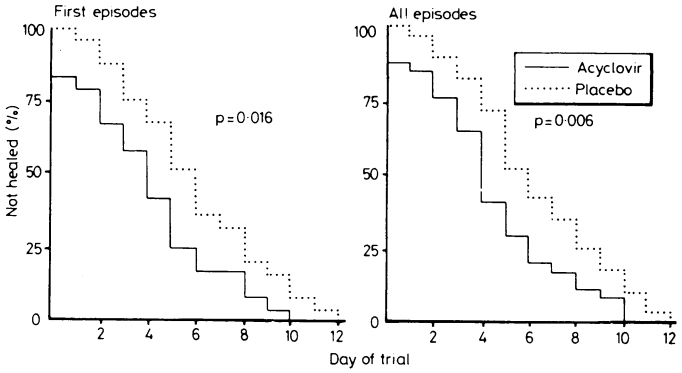
TABLE II—*Effects of acyclovir cream on progression of lesions and symptoms for first and all episodes of herpes labialis*

	First episodes			All episodes		
	Placebo (n = 25)	Acyclovir (n = 24)	p Value	Placebo (n = 40)	Acyclovir (n = 34)	p Value
No (%) of abortive lesions*:						
All patients	2 (8)	8 (33)	0·03	4 (10)	9 (26)	0·06
Those treated before vesicles developed	2/18 (11)	8/19 (42)	0·04	4/26 (15)	9/26 (35)	0·10
No (%) of new lesions	1 (4)	2 (8)	0·52	3 (8)	2 (6)	0·42
No of days to formation of ulcer or crust†:						
All patients	2	1	0·02	2	1	0·04
Excluding those whose lesions aborted‡	2 (23)	2 (16)	0·14	2 (36)	2 (25)	0·16
No of days to healing†						
All patients	6	4	0·02	6	4	0·01
Excluding those whose lesions aborted‡	6 (23)	5 (16)	0·10	6 (36)	5 (25)	0·03
No (%) developing itching	15 (60)	8 (33)	0·06	24 (60)	15 (44)	0·13
Duration of itching (days)†	1	0·5	0·21	1	1	0·15
Duration of all symptoms (days)†	3	1	0·07	2	1	0·11

* Lesions that did not progress beyond the papule stage.
† Median values.
‡ Figures in parentheses represent numbers of patients.

lesions compared with two in the placebo group, whereas for all episodes there were five in the treated group and four in the placebo group.

Acyclovir did not effect the development of new lesions but this was low in both treatment groups. In all patients the time to first formation of ulcer or crust and time to complete healing were significantly reduced in first and all episodes treated with acyclovir (table II and figure). When the patients whose lesions aborted were excluded from the analysis then these two variables still showed trends in favour of acyclovir. For all episodes the time to healing of lesions not aborting was significantly shorter with acyclovir compared with placebo.



Survival curves for time to complete healing of first and all episodes of herpes labialis treated with acyclovir cream or placebo (the occurrence of completely abortive lesions in acyclovir group is responsible for initial separation of curves).

The major symptom reported by the patients was itching, and fewer patients receiving acyclovir developed this symptom during treatment of their first episode. The total duration of all symptoms was also reduced in first episodes treated with acyclovir, though this did not quite reach significance. No other effects on symptoms were shown but symptoms did not play a major part in the course of the infections.

Two patients treated with placebo, four patients treated with acyclovir, and one patient during treatment with both acyclovir and placebo reported flaking of the skin in the area of application of the cream. A further patient receiving placebo reported stinging on application of the cream. Treatment did not have to be withdrawn from any patient.

Discussion

Other workers have reported an antiviral effect in herpes labialis with acyclovir ointment[6] but even increasing the concentration of acyclovir and starting treatment earlier did not apparently improve the results (SL Spruance *et al*, paper presented at 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Miami Beach, 1982). Our study is the first demonstration of a significant clinical benefit with a topically applied antiviral in recurrent herpes labialis. Providing treatment is initiated early in the course of an infection before the damage phase is complete[9] acyclovir cream may be expected to shorten the time to the onset of the ulcer or crust stage, reduce the total healing time by a third, and halve the duration of symptoms. Perhaps more importantly, if treatment can be started before vesicles occur then the proportion of lesions effectively aborting may be increased to a third or more. This means that local tissue damage is negligible and that the skin over the lesions remains intact so lessening the risk of secondary infection or transmission of the virus to contacts. A few more patients receiving acyclovir than placebo reported flaking of the skin and this may be a result of a partially aborted lesion rather than a toxic reaction. Otherwise the treatment was well tolerated.

Although formation of new lesions is rare in herpes labialis, it was observed that topical acyclovir had no effect on new lesions. This is not unexpected, as local applications were limited to the expected site of the initial lesions, but serves to illustrate one of the disadvantages of topical treatment. The use of topical treatment will also be limited in patients with multiple lesions at different sites; lesions in inaccessible places, such as the nares or in the mouth; and where compliance may be a problem, for instance with frequent or continuous usage. Oral acyclovir is effective for recurrent mucocutaneous herpes simplex infections at other sides,[4] and studies evaluating the prophylactic use of oral acyclovir for frequent recurrences of herpes labialis and genital herpes are currently in progress.

For the management of recurrent herpes labialis acyclovir cream offers an effective and acceptable alternative to the unproved home remedies currently attempted.

We thank the nurses of Medical Services, British Petroleum Company Limited, and in particular Sister T Byrne, without whose help this study would not have been possible. We also thank Mrs C A Burke, for performing the statistical analysis and Mr R G Clark, for developing the Clindata program.

References

1 Young SK, Rowe NH, Buchanan RA. A clinical study for the control of facial mucocutaneous herpes virus infections: characterization of natural history in a professional school population. *Oral Surg* 1976; **41**:498-507.

2 Embil JA, Stephens RG, Manuel FR. Prevalence of recurrent herpes labialis and aphthous ulcers among young adults on six continents. *Can Med Assoc J* 1975;**113**:627-30.

3 Brigden D, Fiddian AP, Rosling AE, Ravenscroft T. Acyclovir: a review of the preclinical and early clinical data of a new antiherpes drug. *Antiviral Research* 1981;**1**:203-12.

4 Nilsen AE, Aasen T, Halsos AM, *et al.* Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet* 1982;ii:571-3.

5 Corey L, Nahmias AJ, Guinan ME, Benedetti JK, Critchlow CW, Holmes KK. A trial of topical acyclovir in genital herpes simplex virus infections. *N Engl J Med* 1982;**306**:1313-9.

6 Spruance SL, Schnipper LE, Overall JC Jr, *et al.* Treatment of herpes simplex labialis with topical acyclovir in polyethylene glycol. *J Infect Dis* 1982;**146**:85-90.

7 Juel-Jensen BE. Treatment of erythema multiforme secondary to herpes simplex by prophylactic topical acyclovir. *Br Med J* 1981;**283**:1544.

8 Collins P, Oliver NM. Acyclovir treatment of cutaneous herpes in guinea pigs and herpes encephalitis in mice. *Am J Med* 1982;**73**:96-9.

9 Fiddian AP, Yeo JM, Clark AE. Treatment of herpes labialis. *Journal of Infection* (in press).

10 Ravenscroft T, Smith DE. The development of CLINDATA: a clinical trial data management system. *Journal of Information Science* 1981;**3**: 129-36.

(*Accepted 9 March 1983*)

MEDICINES PROVOKING URINE—The causes by which urine is suppressed are many. 1. By too much drying, or sweating, it may be consumed. 2. By heat or inflammation of the reins or passages whereby it passes from the reins, it may be stopped by compression. Urine is the thinnest part of blood, separated from the thickest part in the reins. If then the blood be more thick and viscous than ordinary, it cannot easily be separated without cutting and cleansing medicines. This is for certain, that blood can neither be separated nor distributed without heat. Yet amongst diuretics are some cold things, as the four greater cold seeds, Winter-cherries, and the like. Although this seem a wonder, yet it may be, and doth stand with truth. For cool diureticks, though they further not the separation of the blood one jot, yet they cleanse and purge the passages of the urine. Diureticks then are of two sorts: 1. Such as conduce to the separation of the blood. 2. Such as open the urinal passages. The former are biting (and are known by their taste) very hot and cutting, whence they penetrate to the reins, and cut the gross humours there. Bitter things, although they be very hot, and cut gross humours, yet are they of a more dry and terrene substance than is convenient to provoke urine. Hence then we may safely gather, that bitter things are not so moist nor penetrating, as such as bite like Pepper. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)