Comparative trial of acyclovir and adenine arabinoside in the treatment of herpes simplex corneal ulcers

JAMES McGIN, PETER TORMEY, AND COLIN B. WALKER
From the Eye Hospital, Southampton, Hampshire

SUMMARY The antiviral acycloguanasine has been compared with adenine arabinoside in the topical treatment of herpes simplex corneal ulcers. It has been found to be at least as good in terms of rate of healing and resolution of symptoms, with ulcers healing in an average of 4-2 days on the acyclovir treatment compared with 6-3 days after adenine arabinoside.

Recent work has shown that the new antiviral acyclovir (acycloguanasine) is a highly effective antiviral drug against the herpes simplex virus.12 It acts mainly on virally infected cells by blocking viral particle formation before the particles pass through the nuclear membrane by means of inhibiting viral DNA polymerase after being converted by virally specific thymidine kinase.4 In tissue culture it has been shown to have an antiviral potency greater than the currently available antivirals.5 It has been successfully used in the treatment of experimental herpes simplex infection,6-9 being at least as effective as idoxuridine and trifluorothymidine.10

Clinically in the topical treatment of dendritic ulcers after minimal debridement it prevents early recurrence,11 is at least as effective as idoxuridine,12,13 and has been successfully used in ulcers due to either idoxuridine or adenine arabinoside clinical resistance.14 Given parenterally it is effective in herpes simplex encephalitis (Punt, personal communication) and herpes simplex infection in patients with malignant disease.15

Currently available antivirals are not always successful in the treatment of herpes simplex corneal ulcers, with failure to heal, sometimes due to viral drug resistance arising,16 hypersensitivity, or topical toxicity occurring. Thus there is a need for a potent antiviral which affects only virally infected cells and has little effect on normal cells. Acyclovir fulfills these criteria, and so in the treatment of herpes simplex corneal ulcers topical acyclovir has been compared with topical adenine arabinoside (ara-A), another active currently available antiviral,17 by means of a comparative randomised clinical trial on 60 patients.

Patients and methods

Patients with a clinical diagnosis of herpes simplex corneal ulcers who were attending the Southampton Eye Hospital were included in this study, if they were able to attend for regular follow-up. Patients with a visual acuity of 6/24, or worse in the uninfected eye, or with other ocular disease were excluded.

The diagnosis of dendritic ulcer was made on clinical grounds, with later confirmation by viral isolation studies where possible.

Treatment in the coded controlled trial was randomly assigned to one of the following groups: (a) acyclovir 3% ointment 5 times a day; (b) adenine arabinoside (ara-A) 3% ointment 5 times a day.

Stratification of treatment was carried out for age, duration of symptoms, and atopy. The groups were divided into those under or over the age of 50, and whether the symptoms had been present for up to 2 weeks, more than 2 weeks, or more than 4 weeks. The size of the ulcer, the presence of any underlying stromal infiltration, or associated uveitis was recorded, together with any history of previous antiviral treatment, prior steroid treatment, or of previous corneal herpes simplex ulceration. A note was taken of any current or past history of herpes cutaneous infection.

The patients were seen either daily or on alternate days until the ulcer had healed, and then 5 days later, and subsequently 3 weeks later. If the ulcer increased significantly in size over 3 successive visits, or failed to decrease in size by the seventh day of treatment, or failed to heal within 14 days of treatment, it was deemed clinically resistant to that particular drug.18 The patient was withdrawn from the study and given alternative antiviral treatment.
Comparative trial of acyclovir and adenine arabinoside in the treatment of herpes simplex corneal ulcers

If the patients were on steroids at entry into the trial, they were weaned off them, with the steroid concentration decreased by log dilutions at 2-weekly intervals.

If the ulcer reappeared at the same site within 14 days of stopping the treatment, the patient was treated with the same coded antiviral agent, and the ulcer was designated a recrudescent ulcer. If an ulcer appeared after 14 days at the same site, it was given the same coded treatment and designated a recurrent ulcer. A new ulcer occurring at a new site was also given the same coded antiviral treatment.

Investigations. At each visit the symptoms of pain, pricking, photophobia, and lacrimation were scored from 0 to 3+. The shape of the ulcer was measured and recorded together with the degree of fluorescein and rose Bengal staining, and any stromal involvement or associated uveitis were recorded. The lids, conjunctiva, and cornea were examined for any possible adverse drug reaction.

At the initial visit swabs were taken for culture of the herpes simplex virus, and inoculated into MRC 5 cell line, and kept at 38°C in tubes on a roller drum.

Results

Of the original 60 patients entering the trial 3 were withdrawn on clinical grounds. Twenty-eight patients received acyclovir and 29 ara-A. The groups were evenly matched in most respects (Tables 1 and 2), their symptoms being present for a similar length of time. Treatment was stratified in terms of symptoms being present for more or less than 2 weeks, and there was an even distribution of patients in these categories between the 2 treatment groups. As ulcers that had been present for 10-14 days might have been healing spontaneously, there could be a bias towards one treatment group if all the ulcers in that group had been present for 14 days and in the other group for only a few days, when the ulcer would still be expected to be enlarging due to viral replication. Therefore each treatment group was broken down into subgroups of days from onset of symptoms. There was no difference between the distribution of the 2 treatments (Table 3).

Table 2  Symptoms at presentation and their resolution (symptoms scored from 0–3+)

<table>
<thead>
<tr>
<th></th>
<th>Mean score at presentation (0–3+)</th>
<th>Mean time to resolve in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Ara-A</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Pain</td>
<td>1.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Photophobia</td>
<td>1.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Grittiness</td>
<td>1.7</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate numbers of patients in which symptom scores had failed to return to zero by the end of the assessment.

The presence of atopy had no effect on the outcome of treatment, nor did the age of the patient. However, there was a significant difference between the groups in terms of the history of recurrent attacks of cutaneous herps (p=0.05, χ² test) (Table 1). There were more than twice as many small ulcers in the ara-A group as in the acyclovir group, and a larger proportion of large or multiple small dendritic ulcers in the acyclovir groups.

All patients receiving acyclovir healed in an average of 4.5 days. One patient receiving ara-A failed to respond. The remainder receiving ara-A healed in an average of 6.2 days (Table 4). But a log rank analysis failed to demonstrate a statistically significant differ-

Table 3  Distribution of treatment: number of patients in each treatment group, with the time symptoms were present before treatment was started

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Days from onset of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-2</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>15</td>
</tr>
<tr>
<td>Ara-A</td>
<td>11</td>
</tr>
</tbody>
</table>

The difference between the rates of healing of the 2 groups is not statistically significant (p>0.05).

Table 4  Outcome and average number of days taken to heal in the 2 groups: treatment with either ara-A or Acyclovir

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Number healed</th>
<th>Days to heal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>28</td>
<td>28</td>
<td>4.5 (SD 2.66)</td>
</tr>
<tr>
<td>Ara-A</td>
<td>29</td>
<td>28</td>
<td>6.2 (SD 1.79)</td>
</tr>
</tbody>
</table>

The difference between the rates of healing of the 2 groups is not statistically significant (p>0.05).

Note designation large ulcers if greater than 3 mm in length.
ence between the 2 groups in terms of healing ratio at
the 5% level (p>0·05) (Table 4).
There was a significant difference though between
the groups in terms of the outcome of symptoms,
which were scored from 0 to 3+. The average scores
at presentation were higher for pain, photophobia,
and grittiness in the acyclovir group and lacrimation
in the ara-A group. All symptoms apart from grittiness
resolved in a shorter time with acyclovir, but only
pain resolved in a statistically shorter time in the
acyclovir group (Table 2).
Prior steroid treatment had no effect on the out-
come of treatment. In the acyclovir group there were
4 such patients. 2 with recrudescence of ulcers occurring 8
and 14 days after initial healing; both subsequently
healed with further topical acyclovir.
Fifteen patients in the acyclovir group had an
associated stromal infiltration, but none required
steroids to suppress this, whereas of 20 patients in the
ara-A group 4 required steroids. The stromal infiltra-
tion, scored from 0 to 3+, had the same average
intensity in each group (1·5 acyclovir group, 1·6
adenine arabinoside group).
An almost similar number in both groups developed
another ulcer or a stromal reaction (disciform keratitis)
at a later date, with a maximum of 21 months’
follow-up (Table 5). Two of these ulcers in the
adenine arabinoside group developed clinical resis-
tance to the drug but successfully healed when treated
with an alternative antiviral.

Table 5  Number of patients with recurrent ulcers or stromal activity after the ulcer healed: follow-up maximum 21 months

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>8</td>
</tr>
<tr>
<td>Ara-A</td>
<td>9</td>
</tr>
</tbody>
</table>

ADVERSE REACTIONS
These were few, despite treatment being continued
for up to 58 days in patients with a subsequent stromal
reaction. A mild punctal keratopathy involving the
conjunctiva in the interpalpebral fissure or lower
fornix was the main clinical sign found. 4 patients in
the acyclovir group and 11 in the ara-A group being
affected. One patient in the ara-A group developed
punctal stenosis. Mild stinging was experienced by 5
patients in each group on instillation of the ointment.

Discussion
Both antiviral agents were effective in the treatment
of dendritic ulcerations. However, although the rate
of healing in the acyclovir group was faster than the
ara-A group, which had a larger number of smaller
dendritic ulcers, the difference was not statistically
significant. As small ulcers heal faster than larger
ulcers, this size difference is of significance and biases
the results against the acyclovir group, which still had
a faster healing rate.
One possible criticism of any clinical antiviral drug
trial is that treatment allocation may not take into
account the duration of symptoms, so that treatment
may be started when viral replication is already on the
wane, and the ulcer spontaneously healing. In support
of this theory herpes virus can be isolated in man in
90% of patients up to 8 days after the onset of
symptoms,19 signifying active viral replication until
then, and in the corneal epithelium up to 7 days after
inoculation of herpes simplex virus into rabbits’
eyes.20 Alternatively, by delaying treatment the virus
could become better established in both the epil-
thelium and stroma, making treatment more difficult.
It has been shown that healing times are quicker if
treatment is begun early after symptoms begin than if
it is started later.21 Therefore treatment allocation
was analysed in terms of days after the onset of
symptoms. There was an equal distribution between
the 2 groups.
Although the pain score in the acyclovir group was
significantly higher, this symptom, together with
photophobia and lacrimation, resolved more quickly
with acyclovir than with ara-A. It is known that
acyclovir penetrates the cornea into the aqueous in
therapeutic levels, and it is of significance that none of
the acyclovir-healed patients required the addition
of steroids during treatment to suppress any stromal
infiltration compared with 4 of the ara-A group who
developed stromal complications requiring steroids.
In a further series of patients topical acyclovir alone
has been successfully used in suppressing the stromal
reaction where there was no overlying dendritic
ulceration.
On follow-up there was an equal number in each
group developing subsequent disciform or stromal
keratitis, and recurrent ulcers. Thus acyclovir does
not appear to have any effect in preventing such
recurrences. It thus resembles other antivirals, which
lead to neither clinical cure nor permanent viral sup-
pression in either animal22 or man.23
Both treatments were well tolerated, and side
effects were few. Punctate keratopathy of the con-
junctiva in the medial palpebral fissure or the lower
fornix was the only side effect seen with either treat-
ment, and there was a higher incidence with ara-A
than acyclovir.
Acylovir appears to have a wide spectrum of
activity against the herpes simplex and herpes zoster
viruses in preliminary clinical studies. It also has been
found to be effective as a topical treatment of herpes
zoster keratouveitis (McGill et al. in press). However,
Comparative trial of acyclovir and adenine arabinoside in the treatment of herpes simplex corneal ulcers

clinical resistance to the drug may well develop, as it acts through the DNA polymerase pathway, for which viral lines with a thymidine kinase deficient system have been found. Indeed in cell culture such isolates are already available,24,25 so that in future the continued use of the drug may possibly lead to resistant strains being found.

We are grateful to our colleagues Mr M. J. Absolon, Mr A. R. Elkington, and Mr I. H. Chisholm for referring patients to this trial, and to Miss Susan Bryder for typing the manuscript.

References