Topical acyclovir in herpes zoster ocular involvement

JAMES McGILL
From the Southampton Eye Hospital, Southampton

Summary  Topical acyclovir has been found in 15 out of 18 patients to control, without recurrences and in an appreciably shorter time than if steroids were used, keratoconjunctivitis induced by herpes zoster. Once steroids were started, recurrences occurred during withdrawal of steroids or after they had been stopped.

Herpes zoster ophthalmica with ocular involvement is a severe, debilitating, painful disease, leading to much ocular damage and visual loss, and frequent postherpetic neuralgia.

So far no drug treatment has been shown definitely to prevent ocular involvement or postherpetic neuralgia or to suppress ocular disease. Topical steroids have an established place in suppressing the ocular signs, but they are unsatisfactory because treatment may be prolonged and in many cases fail to prevent ocular damage. Furthermore, once topical steroid treatment has been stopped, ocular disease may recur, often with further and more severe damage such as corneal opacities with lipid deposition in them, resulting in severe visual loss. Alternative drugs have been suggested in the treatment of this disease, but none have found universal acceptance. Topical antivirals such as idoxuridine and adenine arabinoside have no effect and can be harmful owing to their topical toxicity. Systemic adenine arabinoside has little effect, possibly because of poor drug solubility and tissue penetration. There is a paucity of information on the effect of other antivirals on the ocular involvement of this disease.

For nonocular disease systemic antivirals have been tried. Cytosine arabinoside was initially thought to be effective but was later reported to be ineffective, and in a double-blind trial placebo was found to be superior. Adenine arabinoside has been shown to be effective in immunosuppressed patients, reducing viral isolation times and leading to faster healing but in higher doses it is toxic, suppressing bone marrow function. Systemic steroids have been tried and found to shorten postherpetic neuralgia. But their use carries the risk of systemic spread of the disease, and there is no information on their effect on the eyes. Topical idoxuridine in dimethyl sulphoxide has been used, but the skin toxicity of both substances must be of concern. Amantadine has been found in a multicentre trial to shorten postherpetic neuralgia, but there was no mention of its effect on ocular involvement. Systemic interferon significantly lessened the disease’s severity in patients with malignant disease, but there was little information on its effect on ocular involvement. Thus there is a need for an effective drug for treating the ocular involvement of this disease.

The new antiviral acyclovir, a cyclic nucleoside, has a high specificity for virally infected cells, with little effect on uninfected cells, and it has been shown to be effective in treating herpes simplex ocular disease. In tissue culture it has been found to be effective against herpes zoster virus, with inhibition of DNA synthesis though it is not as effective as against the herpes simplex virus. In immunosuppressed patients with herpes zoster skin infection systemic acyclovir has had a favourable effect.

The drug has a high solubility, and after topical ocular application therapeutic aqueous levels have been found (D. Brigden, personal communication). Thus acyclovir appears to have clinical potential against herpes zoster infections, and has been used on an open basis in the topical treatment of herpes zoster ocular involvement.

Patients and methods

This study was on 21 consecutive patients who had ocular herpes zoster and in whom the skin rash had subsided within the last 28 days. Patients were...
Table 1  Individual patient responses to topical acyclovir 3%

![Table 1](http://bjo.bmj.com/)

Patients 12, 15, and 16 had had prior intravenous acyclovir (5 mg/kg intravenously 3 times a day). Patients 5, 9, and 14 required topical steroid\(^*\) added to this regimen later on, as their uveitis increased in severity despite topical acyclovir.

Table 2  Average duration of the individual signs and of treatment in 15 patients treated with acyclovir

![Table 2](http://bjo.bmj.com/)

*Results*

In 18 patients topical acyclovir alone was initially used, and it controlled the ocular disease in 15 out of them, with quick resolution of signs of the disease. In 3 patients there was an increase in the severity of the uveitis despite topical acyclovir, and topical steroids were required to suppress the signs of the uveitis (see Table 1 for details of individual patients). The average duration of treatment for those patients treated only with topical acyclovir was 12.2 weeks (Table 2).
In the 3 patients who required topical steroids, and in 3 others who were on topical steroids before acyclovir was begun, treatment was prolonged, and in all of them the ocular disease flared up as soon as the steroids were tapered off. The disease recurred once treatment had been stopped. The average duration of treatment for this group was much longer at 27 weeks (Tables 3 and 4).

None of the patients treated with just acyclovir had a recurrence of the disease once the acyclovir had been tapered off; the average follow-up was 35 weeks. All the patients treated with steroids and acyclovir had a recurrence. In this latter group the follow-up has been shorter, as the treatment has been more prolonged (Table 5).

### Discussion

Herpes zoster ophthalmicus is a variable disease, so that it is difficult in an open trial to reach any definite conclusions on the effect of acyclovir on its course. However, in 15 out of 18 of those patients treated only with topical acyclovir the ocular involvement subsided, treatment was comparatively short, and permanent ocular damage minimal. There were no recurrences after treatment had been stopped in the group started on acyclovir with no prior steroids.

It is said that the peripheral corneal ulceration normally associated with herpes zoster infection often spontaneously heals. However, the average resolution of 5-2 days reported here compares favourably with that of 11 days reported by Piebenga and Laibson.

Herpes zoster keratouveitis can often subside without the addition of steroids. The results can be criticised on the grounds that steroids were given in addition only to those patients with a severe ocular disease, and that acyclovir itself was given only to those patients with mild

### Table 3
Individual patient responses to steroids and topical acyclovir

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Sex</th>
<th>Rash present (days)</th>
<th>Ulcer healed (days)</th>
<th>Stroma resolved (days)</th>
<th>Uveitis settled (days)</th>
<th>Glaucoma settled (days)</th>
<th>Recurrence</th>
<th>Duration of treatment (weeks)</th>
<th>Follow-up (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>60</td>
<td>F</td>
<td>28</td>
<td>—</td>
<td>—</td>
<td>28</td>
<td>28</td>
<td>Yes</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>83</td>
<td>F</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>16</td>
<td>63</td>
<td>Yes</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>14</td>
<td>32</td>
<td>M</td>
<td>9</td>
<td>4</td>
<td>21</td>
<td>77</td>
<td>—</td>
<td>Yes</td>
<td>25</td>
<td>10</td>
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<tr>
<td>19</td>
<td>85</td>
<td>F</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>44</td>
<td>2</td>
<td>Yes</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>25</td>
<td>78</td>
<td>F</td>
<td>2</td>
<td>10</td>
<td>77</td>
<td>45</td>
<td>7</td>
<td>Yes</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>21</td>
<td>31</td>
<td>M</td>
<td>5</td>
<td>9</td>
<td>20</td>
<td>25</td>
<td>—</td>
<td>Yes</td>
<td>33</td>
<td>15</td>
</tr>
</tbody>
</table>

Patients 5, 9, and 14 had steroids added to their regimen, as their uveitis worsened on topical acyclovir. Patients 19, 20, and 21 were already on steroids when acyclovir was started.

### Table 4
Average duration of individual signs and length of treatment in 6 patients treated with steroids and acyclovir

<table>
<thead>
<tr>
<th>Ulcer</th>
<th>Stromal infiltration</th>
<th>Episcleritis</th>
<th>Uveitis</th>
<th>Treatment duration</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>4 (6)</td>
<td>5 (7)</td>
<td>— (8)</td>
<td>6 (9)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Average time (Days)</td>
<td>6-25 (13)</td>
<td>26 (14)</td>
<td>— (15)</td>
<td>39-1 (16)</td>
<td>27 (17)</td>
</tr>
</tbody>
</table>

### Table 5
A comparison of average duration (in days) of individual signs, treatment duration, and follow-up times (in weeks) in the 2 groups on acyclovir and steroids + acyclovir

<table>
<thead>
<tr>
<th>Group</th>
<th>Number in group</th>
<th>Ulcer (days)</th>
<th>Stromal infiltration (days)</th>
<th>Episcleritis (days)</th>
<th>Uveitis (days)</th>
<th>Treatment duration (weeks)</th>
<th>Follow-up (weeks)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without steroids</td>
<td>15</td>
<td>5-4</td>
<td>16-6</td>
<td>16-4</td>
<td>21</td>
<td>12-2</td>
<td>35-1</td>
<td>0</td>
</tr>
<tr>
<td>With steroids</td>
<td>6</td>
<td>6-25</td>
<td>26</td>
<td>—</td>
<td>39-1</td>
<td>27</td>
<td>17-6</td>
<td>6</td>
</tr>
</tbody>
</table>
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ocular involvement which would have spontaneously resolved without treatment. However, the quick resolution of acyclovir treated patients and the lack of recurrences was significant. But the only way to answer the problem definitely is by means of a randomised coded trial comparing topical acyclovir with topical steroids, and this is now under way.

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References

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J. McGill

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