Acute herpes zoster and postherpetic neuralgia: effects of acyclovir and outcome of treatment with amitriptyline

DAVID BOWSHER

SUMMARY. This retrospective study was designed to assess the effects of acyclovir treatment of acute herpes zoster on subsequent postherpetic neuralgia, and to examine the effects of amitriptyline in the treatment of postherpetic neuralgia. Eighty seven patients with postherpetic neuralgia of three or more months' duration were studied: 24 of them had had herpes zoster treated with oral acyclovir. At first presentation, only 25% of the patients had not received acyclovir. A higher proportion of patients who had had acyclovir than had not selected the word group containing burning on the McGill pain questionnaire compared with 78% of the patients who had not received acyclovir. Acyclovir thus appears to change the nature of postherpetic neuralgia. Postherpetic neuralgia was treated with amitriptyline, alone or in combination with distigmine and/or sodium valproate. There was a strong correlation between pain relief and the interval between the occurrence of herpes zoster and the initiation of treatment with amitriptyline—early treatment is almost twice as likely to be successful as late. Since conventional analgesics and sympatholytic drugs are of no benefit in the treatment of established postherpetic neuralgia, the sequelae of herpes zoster must, therefore, be recognized and treated with amitriptyline as soon as possible.

Keywords: herpes zoster; neuralgia; complications; antiviral agents; antidepressive agents; management of pain.

Introduction

Herpes zoster is by far the commonest disease affecting the nervous system, with an annual incidence of four cases per 1000 people in the United States of America. The disease occurs mainly in elderly people, and is followed by postherpetic neuralgia in some 25% of cases overall. This figure increases with advancing age such that in patients over the age of 70 years the incidence of postherpetic neuralgia rises to 75%. Postherpetic neuralgia, which can persist for life, is rated by patients as one of the most intense forms of chronic pain. It is characterized not only by analgesic-resistant pain, but by an area of sensory deficit within which the pain is experienced. The deficit particularly affects small fibre modalities (warm, cold and pinprick) with the notable exception of hot pain. Alloodynia (pain induced by a non-painful stimulus, such as stroking) occurs in some 90% of cases; indeed, it is alloodynia which proves to be the main problem in the majority of persistent cases, usually because of the movement of clothing across the body or wind across the face. As herpes zoster and postherpetic neuralgia usually form a temporal continuum, the arbitrarily agreed transition point from herpes zoster to postherpetic neuralgia is one month after the appearance of the rash.

The aim of this retrospective analysis was to assess the effects of acyclovir treatment of acute herpes zoster on subsequent postherpetic neuralgia, and to examine the effects of amitriptyline in the treatment of postherpetic neuralgia.

Method

All successive patients with postherpetic neuralgia of more than three months' duration who had been diagnosed and treated at the Mersey Regional Centre for Pain Relief over the two year period 1988–90 were considered for inclusion in the study. Patients who had had postherpetic neuralgia for less than three months when first seen at the clinic were initially excluded from the study as many cases of early persistent pain appear to get better spontaneously. If the postherpetic neuralgia continued they were included later. Patients who had received drugs which suppress the immune system or who were known to suffer from an immunosuppressive condition were excluded as were those whose treatment of herpes zoster with acyclovir had begun more than three days after the appearance of the vesicles or after the rash had ceased to suppurate if this was less than three days after the appearance of the vesicles. All patients had been treated for herpes zoster by their general practitioner, and were not seen in the clinic until referred with postherpetic neuralgia.

All cases of postherpetic neuralgia were treated in the clinic with amitriptyline, mostly alone, or in combination with distigmine and/or sodium valproate.

Patients were sent a McGill pain questionnaire with their appointment letter; if it had not been completed on arrival at the clinic, a research nurse helped the patient to fill in before the patient was seen by the consultant. The questionnaire contains 20 groups of from two to six words, and patients are asked to underline not more than one word in any group which applies to the pain which is being experienced, ignoring those word groups which are inapplicable. The first 10 groups of words are somatic, that is they describe the possible physical qualities of the pain. Of these 10 somatic groups, the tenth starts with the word 'tender'. This word is always underlined by patients seeking to describe allodynia, from which 90% of patients with postherpetic neuralgia suffer, so the results here are confined to the first nine groups.

Pain intensity was recorded by the visual analogue method at the first and subsequent visits. In this method, patients were asked to make a mark on a line at whose left hand end was printed 'No pain at all' and at the right hand end 'The worst pain I ever felt'. The mark should represent the intensity of pain the patient feels at the time. The line is 100 mm long. The distance in millimetres of the patient's mark from the left hand end of the line is taken to represent pain intensity as a percentage.

Results

Of the 87 patients included in the study, six were aged 50–60 years when herpes zoster was contracted; the rest were over 60 years of age. The area affected by herpes zoster was the trigeminal nerve in 26% of cases (including one case where the maxillary nerve only was affected, one where the mandibular

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nerve only was affected, one where the maxillary and mandibular nerves only were affected, and one where all three nerves were affected; the neck in 14% of cases; the thorax in 55%; and the lumbosacral region in 5%. Twenty four patients had had their herpes zoster treated with systemic acyclovir 800 mg five times a day for seven days. For four of these patients the trigeminal nerve was the site affected by the herpes zoster, for four the neck, for 14 the thorax, and for two the lumbosacral region.

Pain intensity was measured at the initial interview for 19 patients who had received acyclovir treatment and all 63 patients who had not. The median pain intensity measured on the visual analogue scale at presentation was 90% for the patients who had received acyclovir treatment and 95% for those who had not. The words on the McGill pain questionnaire chosen by the patients to describe their pain are shown in Table 1. While the proportions of patients choosing particular descriptions or groups of descriptions are fairly similar for the two groups, the words in group seven were chosen three times more frequently by the patients whose herpes zoster had not been treated with acyclovir.

Among the 24 patients who had received acyclovir treatment 19 had received treatment for postherpetic neuralgia for three months or more at the time of writing. The remaining five patients had received treatment for less than three months. All 63 patients who had not received acyclovir treatment had received amitriptyline treatment for three months or more. There were no statistically significant differences between cases treated with amitriptyline alone or in combination with distigmine and/or sodium valproate so all therapeutic effects reported here will be attributed to amitriptyline.

The 63 patients who had not received acyclovir treatment were subdivided into those whose pain was improved following amitriptyline treatment (36 patients (57%), median score on visual analogue scale reduced from 90% to 60%) and those who did not respond after three months of therapy or more (27 patients). Among the 19 patients who had received acyclovir treatment and amitriptyline treatment for postherpetic neuralgia for three months or more, pain had improved for 14 patients (74%, median score on visual analogue scale reduced from 90% to 50%).

Statistical analysis using Student's t test showed no significant difference between the mean age of patients who received acyclovir and those who did not (70.3 years and 70.2 years, respectively); nor within the latter group between those whose pain was improved by amitriptyline treatment and those whose pain was not improved (69.3 years and 71.5 years, respectively). The interval between the onset of acute herpes zoster and commencement of treatment of postherpetic neuralgia is shown in Table 2. The ranges show that in some instances, treatment initiated at three months did not prove successful. However, further analysis of the data for the 63 patients who did not receive acyclovir treatment shows that of the 25 patients who received amitriptyline treatment between three and 12 months after the onset of acute herpes zoster 76% were improved (reduction of pain score by 50% or more); of the 15 for whom treatment began after 13-24 months, 53% were improved; and of the 23 for whom amitriptyline treatment was commenced after 25 months or more, only 39% improved.

For patients who had and had not received acyclovir treatment but who had experienced the same interval between the onset of herpes zoster and the commencement of amitriptyline treatment (10 patients in each group) there was no significant difference in the length of time over which the pain score fell by at least 75%.

### Table 1. Sensory word groups from McGill pain questionnaire most frequently chosen by patients at first visit.

<table>
<thead>
<tr>
<th>McGill word group</th>
<th>No. (%) of patients</th>
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<tbody>
<tr>
<td></td>
<td>Treated with acyclovir (n = 24)</td>
</tr>
<tr>
<td>1. Flickering, quivering, pulsing, throbbing, beating, pounding</td>
<td>11 (46)</td>
</tr>
<tr>
<td>2. Jumping, flashing, shooting</td>
<td>8 (33)</td>
</tr>
<tr>
<td>3. Pricking, boring, drilling, stabbing, lancinating</td>
<td>13 (54)</td>
</tr>
<tr>
<td>4. Sharp, cutting, lacerating</td>
<td>8 (33)</td>
</tr>
<tr>
<td>5. Pinching, pressing, gnawing, cramping, crushing</td>
<td>6 (25)</td>
</tr>
<tr>
<td>6. Tugging, pulling, wrenching</td>
<td>3 (13)</td>
</tr>
<tr>
<td>7. Hot, burning, scalding, searing</td>
<td>6 (25)</td>
</tr>
<tr>
<td>8. Tingling, itching, smarting, stinging</td>
<td>13 (54)</td>
</tr>
<tr>
<td>9. Dull, sore, hurting, aching, heavy</td>
<td>15 (63)</td>
</tr>
</tbody>
</table>

n = number of patients in group.

### Table 2. Interval between onset of herpes zoster and commencement of treatment for postherpetic neuralgia.

<table>
<thead>
<tr>
<th>Interval between onset of herpes zoster and amitriptyline treatment (months)</th>
<th>Patients treated with amitriptyline (n = 24)</th>
<th>Pain score reduced by amitriptyline (n = 36)</th>
<th>Pain score not reduced by amitriptyline (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SE)</td>
<td>5.7 (0.5)</td>
<td>23.3 (4.4)</td>
<td>37.3 (6.9)</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Range</td>
<td>3-12</td>
<td>3-96</td>
<td>3-180</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>4.6 to 6.7</td>
<td>14.3 to 32.4</td>
<td>23.1 to 51.5</td>
</tr>
</tbody>
</table>

n = number of patients in group. SE = standard error.

### Discussion

A number of features stand out clearly from this survey. First, the nature of postherpetic neuralgia is changed by acyclovir treatment of acute herpes zoster. Burning and shooting are normally the characteristic descriptions of neurogenic pains, including postherpetic neuralgia, as well as conditions such as painful diabetic neuropathy and central post-stroke pain. However, only 25% of the 24 patients who had received acyclovir treatment selected the word group containing burning on the McGill pain questionnaire; the largest proportions chose words in groups three, eight and nine. The category containing the word shooting was selected by only 33% of patients who had received acyclovir treatment compared with 51% of those not receiving the drug.

Secondly, response to amitriptyline treatment was more likely to be successful the shorter the interval between acute herpes zoster and the initiation of amitriptyline treatment for postherpetic neuralgia, as demonstrated by Bhala and colleagues in a previous series of patients. The results of this treatment are far from ideal, but are consistently better than those achieved by any other available therapy and would obviously be improved by earlier treatment with amitriptyline.

All patients with postherpetic neuralgia seen at the clinic will have been given conventional analgesics, ranging from paracetamol through buprenorphine to morphine, for their pain...
by their general practitioner. Neurogenic pain is not relieved by these drugs, which is why in many instances progressively stronger narcotics are unsuccessfully prescribed. Many patients with established ophthalmic or cervical postherpetic neuralgia are subjected to stellate ganglion blockade, sometimes on more than one occasion. This procedure rarely produces relief for more than a few hours.

Whether all cases of acute herpes zoster should be treated with systemic acyclovir is not a question which can be answered by the results of this investigation. A number of patients have been seen at the clinic whose herpes zoster had been unsuccessfully treated with topical acyclovir cream, and this would appear to be an expensive waste. When a satisfactory vaccine becomes available, it may prove possible to prevent herpes zoster altogether, and therefore postherpetic neuralgia, by vaccinating all infants against varicella zoster at the same time as for other childhood exanthemata.

What is more important at present is that the sequelae of herpes zoster should be recognized and treated with amitriptyline as soon as possible. All patients with herpes zoster should be asked to report to their general practitioner six weeks after the initial diagnosis has been made, to determine whether or not they still have pain in the area of the original herpes zoster. If the answer is positive, then treatment with amitriptyline, with or without diltiazem and/or sodium valproate, should be initiated immediately.

References


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