Divalproex sodium in the management of post-herpetic neuralgia: a randomized double-blind placebo-controlled study


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Summary

Background: Post-herpetic neuralgia is difficult to treat. Divalproex sodium (valproic acid and sodium valproate in molar ratio 1:1) has been used successfully in the management of various painful neuropathies.

Aim: To study the effectiveness and safety of divalproex sodium in the management of post-herpetic neuralgia.

Design: Randomized double-blind placebo-controlled trial.

Methods: We enrolled 48 consecutively attending out-patients with post-herpetic neuralgia, out of whom three were excluded (two had insufficient pain, one withdrew consent). Quantification of pain was by Short Form-McGill pain questionnaire (SF-MPQ), visual analogue scale (VAS), present pain intensity score (PPI) and 11 point Likert scale (11 PLS) at the beginning of the study, after 2 weeks, 4 weeks and at the end of the study (8 weeks). We also assessed patients’ global impression of change by questionnaire at the end of the study.

Results: After 8 weeks treatment with 1000 mg/day divalproex sodium, there was significant reduction in pain: SF-MPQ, 20.47 ± 2.29 to 11.90 ± 6.52 (p < 0.0001); PPI 4.0 ± 0.52 to 1.95 ± 1.29 (p < 0.0001); VAS 70.17 ± 9.21 to 31.27 ± 29.74 (p < 0.0001) and 11 PLS 6.97 ± 0.73 to 3.63 ± 2.34 (p < 0.0001) in comparison to placebo (means ± SEM). The ‘global impression of change’ questionnaire showed much or moderate improvement in pain in 58.2% of patients receiving divalproex vs. 14.8% of those receiving placebo. The drug was well tolerated by all patients, except one who developed severe vertigo after 10 days of treatment.

Discussion: Divalproex sodium provides significant pain relief in patients of post-herpetic neuralgia, with very little incidence of adverse reactions. These data provide a basis for longer trials in a larger group of patients.

Introduction

Post-herpetic neuralgia (PHN) is the most commonly reported sequelae of herpes zoster for which many definitions have been proposed. The most common definition of PHN is the presence of pain for more than one month after eruption of the rash; however, many clinicians have considered a duration of >6 months as PHN.1-3 The severity of PHN is related to patient age, number of dermatomes involved, severity of pain during the acute phase of zoster and prodromal sensory symptoms.4,5 It requires medical attention because of its significant effect on the quality of life.

Important drug interventions in the management of PHN include the use of non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and anticonvulsants. Amitriptyline reduces burning, aching, sharp throbbing and stinging pain, but its use in elderly patients with heart block, obstructive
uropathy, orthostatic hypotension or narrow-angle glaucoma requires caution because of its dose-related side-effects. The combined use of fluphenazine and amitriptyline causes excessive sedation and tardive dyskinesia. Carbamazepine and diphenylhydantoin have been used for a long time, but they have their own limitations due to haematological and central nervous system side-effects. Gabapentin monotherapy appears to be efficacious for the treatment of pain and sleep interference associated with PHN, but has sedation and ataxia as major adverse effects. Topical therapy, including the local application of anaesthetics, nonsteroidal anti-inflammatory drugs (NSAID), aspirin with chloroform and capsaicin, are either unproven in long-term use or not commonly available.

Valproates have been successfully used in painful conditions such as diabetic neuropathy, migraine and trigeminal neuralgia. As the available treatment modalities of PHN are not completely satisfactory, we investigated the effect of divalproex sodium in PHN.

Methods

Patient and control selection

After explaining the nature of study in detail, a consent form was given to all the PHN patients, and the first 48 consecutive attenders who gave consent were included in the trial. Allocation of numbers and decoding was done by the statistician. Three patients were later excluded from the study: two had insufficient pain score on subsequent examination (visual analogue scale <40) and one withdrew consent. The medicines were dispensed to the patients by nursing staff in packets containing sufficient drug to last for 8 weeks, bearing a distinctive code. Randomization was done as reported in our earlier study. All patients were subjected to detailed clinical and neurological examination, and the quantification of severity of pain was done using the Short Form McGill pain questionnaire (SF-MPQ), present pain intensity score (PPI), visual analogue scale (VAS) and 11-point Likert scale (11 PLS) at the beginning of the study and at every follow-up visit.

Statistical analysis

The demographic characteristics and data of both groups were recorded. All biochemical values (fasting blood glucose, blood urea, serum creatinine, serum bilirubin, AST/ALT) were expressed as means ± SEM. Response of drug/placebo was compared statistically in relation to duration of treatment (2nd week, 4th week, 8th week of treatment). The comparison of data for the two groups was by ANOVA and MANOVA. The post-hoc comparison used Tukey’s HSD for unequal numbers with SPSS (version 7.0).

Results

Clinical data

Of the 24 patients enrolled in each group, 22 (91.66%) in group A and 18 (75%) in group B completed the study (Figure 1). The demographic data of patients of both group showed non-statistical differences in age, sex and duration of post-herpetic...
neuralgia (Table 1). Details of the topographic distribution of herpes zoster lesions are shown in Table 2. At the end of treatment, the patients receiving divalproex sodium (group A) reported significant improvement in pain, compared to the placebo group (B), as measured by SF-MPQ, PPI, VAS and 11 PLS ($p < 0.0001$) (Table 3, Figure 2). The NNT (calculated by VAS parameters) for at least 50% pain relief compared with placebo was 2 (Table 4).

The results of patients’ ‘Global impression of change’ questionnaire at the end of 8 weeks revealed much or moderate improvement of pain in 58.2% patients receiving divalproex sodium, in comparison to 14.8% patients receiving placebo. However, 67.8% of patients receiving placebo and 21.8% of those treated with divalproex sodium reported no change in pain score (Figure 3).

**Table 1** Baseline characteristics of the patients enrolled in the study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (drug)</th>
<th>Group B (placebo)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>22</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>57.96 ± 10.80</td>
<td>56.36 ± 9.28</td>
<td>0.30</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>12:10</td>
<td>10:8</td>
<td></td>
</tr>
<tr>
<td>Duration of PHN (months)</td>
<td>7.7 ± 2.36</td>
<td>8.04 ± 2.69</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**Table 2** Distribution of lesions

<table>
<thead>
<tr>
<th>Segment of zoster</th>
<th>Group A ($n=22$)</th>
<th>Group B ($n=18$)</th>
<th>Total ($n=40$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic</td>
<td>12 (54.5%)</td>
<td>10 (55.5%)</td>
<td>22 (55.0%)</td>
</tr>
<tr>
<td>Trigeminal</td>
<td>6 (27.2%)</td>
<td>5 (27.7%)</td>
<td>11 (27.5%)</td>
</tr>
<tr>
<td>Cervical</td>
<td>2 (9.0%)</td>
<td>2 (11.1%)</td>
<td>4 (10.0%)</td>
</tr>
<tr>
<td>Misc.</td>
<td>2 (9.0%)</td>
<td>1 (5.5%)</td>
<td>3 (7.5%)</td>
</tr>
</tbody>
</table>

**Safety profile of the drug**

Three patients complained of nausea, dizziness, drowsiness, and mild change in appetite, which gradually subsided over a period of 3–5 days and did not require stopping of the drug. One patient (on drug) complained of severe vertigo after 10 days of treatment and was discontinued from the study. All other patients tolerated the drug well.

**Discussion**

This hospital-based (out-patient department) randomized double-blind placebo-controlled study assessed the efficacy and safety of divalproex sodium in 48 cases of PHN, with quantification of pain by SF-MPQ, PPI, VAS, 11 PLS and a ‘global impression
of change’ questionnaire. The demographic data of patients receiving drug and placebo did not show any statistically significant difference. However, disparity in the educational status of patients filling in the pain questionnaire may be a source of potential bias in this study.

Various therapeutic options are available for the treatment of PHN, but none has a satisfactory therapeutic and adverse effect profile. PHN produces severe pain, and at times it may be refractory to all available therapy. Topical therapy includes use of local anaesthetics, non-steroidal anti-inflammatory agents and aspirin with chloroform, which are either of unproven value in long-term management, or are not commonly available. Topical capsaicin produces a modest improvement in pain after long term use, but has a high intensity of burning sensation, which is usually unacceptable. Topical aspirin dissolved in chloroform is quite an effective mean of reducing pain associated with herpes zoster but has adverse effects.

Table 3 Change in pain scores from baseline to end of treatment

<table>
<thead>
<tr>
<th>Pain score</th>
<th>Group A (n=22)</th>
<th>Group B (n=18)</th>
<th>A vs. B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End point</td>
<td>Baseline</td>
</tr>
<tr>
<td>SF-MPQ</td>
<td>20.47 ± 2.29</td>
<td>11.90 ± 6.52</td>
<td>18.13 ± 3.02</td>
</tr>
<tr>
<td>PPI</td>
<td>4.0 ± 0.52</td>
<td>1.95 ± 1.29</td>
<td>3.68 ± 0.56</td>
</tr>
<tr>
<td>VAS</td>
<td>70.17 ± 9.21</td>
<td>31.27 ± 29.79</td>
<td>63.18 ± 9.18</td>
</tr>
<tr>
<td>11 PLS</td>
<td>6.97 ± 0.73</td>
<td>3.63 ± 2.34</td>
<td>6.13 ± 0.94</td>
</tr>
</tbody>
</table>

Data are means ± SEM.

Table 4 Number needed to treat (NNT) calculated using VAS as a parameter for pain relief

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total number of patients treated</th>
<th>Number who achieved at least 50% pain relief</th>
<th>Number who did not achieve at least 50% pain relief</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex sodium</td>
<td>22</td>
<td>13</td>
<td>9</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Placebo</td>
<td>18</td>
<td>2</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Effect on different pain scores. *p value <0.0001 for all pain scores.
Opioids are frequently used to treat PHN in clinical practice, but do not have adequate support from placebo-controlled studies for long term use.

Different tricyclic antidepressants (TCAs) either as monotherapy or in combination are effective, but are not considered safe. They are poorly tolerated by the elderly, with excessive sedation, cognitive impairment, dry mouth, constipation, sexual dysfunction and orthostatic light-headedness. Gabapentin monotherapy appears to be efficacious for the treatment of pain and sleep interference associated with post-herpetic neuralgia, and exhibits positive effects on mood and quality of life, but side-effects including dizziness and somnolence are observed in nearly 25% of patients. Anticonvulsant drugs have been used in pain management for a long time. Divalproex sodium has been successfully used in migraine prophylaxis, and in a recently published study, sodium valproate was very useful in the management of painful diabetic neuropathy. It also had a uniquely favourable side-effect profile.

Valproic acid inhibits GABA transaminase (aminotransferase) and succinic semialdehyde dehydrogenase enzymes involved in the synthesis and degradation of GABA, thereby decreasing GABA metabolism and thus increasing GABA level. It also prolongs the recovery of voltage-gated sodium channels. Thus valproic acid has effects on both neurotransmitter and neuromodulator pathways related to neuropathic pain, which theoretically should make it more effective than drugs such as carbamazepine or phenytoin that mainly act only on neuronal membrane ion channels.

After 8 weeks treatment with divalproex sodium, we observed significant reductions in the different pain scores SF-MPQ, PPI, VAS and 11 point Likert scale, and all the values were statistically highly significant. We did not find any other study in the literature using divalproex sodium in the treatment of PHN, but Rowbotham et al. used gabapentin in a similarly designed study. They also observed highly significant changes in SF-MPQ (17.2 ± 9.6 to 11.4 ± 9.3, p < 0.001), PPI (4.3 ± 2.8 to 2.4 ± 2.5, p < 0.01) and 11 PLS (6.3 ± 1.6 to 4.2 ± 2.3, p < 0.001). The pain relief from divalproex sodium appears to be comparable to that from gabapentin. As drug tolerance side-effects are concerned, the divalproex was very well tolerated and only one had side-effects sufficient to warrant stopping the drug. In contrast, Rowbotham et al. observed severe side-effects of gabapentin in 25% of patients, and 18.6% of the patients could not complete the study.

At the end of study, 58.2% patients treated with divalproex sodium categorized their pain as much or moderately improved, in comparison to 14.8% patients treated with placebo. The majority of patients (67.8%) receiving placebo reported no change in their level of pain, compared to 21.8% of patients receiving divalproex sodium (Figure 2). Rowbotham et al. reported that 43.2% of patients receiving gabapentin showed much or moderate improvement in pain, in comparison to 12.1% patients receiving placebo. The majority of patients (59.5%) receiving placebo reported no change in their level of pain, compared to 22.9% of those receiving gabapentin. No similar study using divalproex sodium in PHN was available for comparison.

We observed a significant subjective improvement in pain in PHN patients receiving divalproex sodium, in comparison to placebo, at the end of 8 weeks, with moderate side-effects in only one
patient. These data provide a basis for a future study in a larger group of patients with a longer duration, to study the effect of divalproex sodium in the management of post-herpetic neuralgia.

References