Effectiveness of oxcarbazepine in symptomatic treatment of painful diabetic neuropathy

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Background: Both basic and clinical research has demonstrated that antiepileptic drugs can be effective in alleviating neuropathic pain. It was hypothesized that oxcarbazepine might be effective in reducing the symptoms of painful diabetic neuropathy. Aims: To investigate the long-term efficacy and safety of oxcarbazepine in symptoms of painful diabetic neuropathy. Materials and Methods: This study included thirty-eight painful diabetic neuropathy patients, which were screened with clinical assessment and electrophysiological studies. The efficacy and safety of oxcarbazepine were evaluated according to the changes in pain intensity and social interference subitems scores of Short-form Brief Pain Inventory besides electrophysiological studies at the end of six months of the treatment. Statistical Analysis: The Students t, Mann-Whitney U and Rank Sum test and Chi-square tests were applied to examine variables differences. The level of statistical significance was chosen to be \( P < 0.05 \). Results: A significant difference was found in all of subitems of pain intensity and social interference at the end of the study according to the baseline scores. Improvement was observed in 52.7%, 63.1%, 55.3% and 63.2% of patients for worst, least, average and pain right now at the end of six months, respectively. Improvement was observed as 60.6%, 63.2%, 52.6%, 60.5%, 68.4% and 63.2% for general activity, mood, walk, work, people relations, sleep and life enjoyment subitems, respectively. None of these patients had any prominent side effect leading to discontinue the treatment. Conclusion: Long-term oxcarbazepine treatment was found to be effective and safe in the symptoms of painful diabetic neuropathy.

Key words: Oxcarbazepine, pain, diabetes mellitus, neuropathy, treatment, brief pain inventory, electrophysiology, quality of life.

Introduction

The complex pathophysiology and difficult-to-treat nature of diabetic neuropathy symptoms remains an important clinical challenge. A large number of drugs with different mechanisms of action on pain symptoms of diabetic neuropathy have been tried such as certain anticonvulsants, antidepressant drugs or local anesthetics.\[1-12\] Because of the limitations of the available treatment modalities, new agents that are effective and safe need to be search for patients with diabetic neuropathy. Oxcarbazepine is one of the new derivatives of anti-epileptic agents. Although its pharmacodynamical effects are similar to carbamazepine, the profile of oxcarbazepine has lack of side effects common to carbamazepine. Thus, we aimed to investigate long-term efficacy and safety of oxcarbazepine in painful diabetic neuropathy.

Materials and Methods

The study was conducted in Department of Neurology, Faculty of Medicine, between December 2003 and December 2004. The Ethics Committee of Medical School approved the study. All patients were required to sign an informed consent before participation in the study.

Patients with type II diabetes mellitus were eligible for the study. All patients were receiving oral anti-diabetic medication during under the care of an endocrinologist. Diabetes mellitus was diagnosed as recommended by American Diabetes Association.\[13\] Patients with glycosylated hemoglobin less than 6.7% at the initial evaluation and patients with causes of neuropathy other than diabetes mellitus were ineligible.

A detailed medical history was obtained and an electrocardiogram was performed at the screening visit. Clinical laboratory tests (hematology, blood chemistries including electrolytes, glucose, lipid profile, liver, renal and thyroid function tests, total glycosylated hemoglobin and urinalysis) were performed.
at the beginning of the study and the final visit at the sixth month. Plasma glucose and HbA1C levels also were measured before and at the end of the treatment phase. There was no significant change in HbA1C over the treatment period.

Patients were enrolled into the study if they are eligible for the followings:

1. Ages between 18 to 65 years
2. Distal symmetrical polyneuropathy was indicated by medical history, neurological examination and abnormal nerve conduction test results (Michigan Neuropathy Screening Instrument)
3. Pain attributed to diabetic neuropathy had been present for at least 6 months
4. A mean pain intensity of at least four on a 10-point numerical pain scale (VAS 0 to 10 0 means no pain, 10 means the worst imaginable pain) and
5. Patients with serum sodium levels between 134 and 146 mEq/L at baseline were enrolled.

Patients were excluded from participation for any of the following reasons:

1. Known contraindication to or prior use of any anticonvulsant
2. Peripheral neuropathy attributable to other causes such as alcoholism, connective tissue disease, or toxic exposure
3. Severe depression
4. Estimated creatinin clearance <30 mL/min or elevated levels of liver enzymes
5. Clinically significant cardiovascular, renal, or hepatic disease conditions
6. History of narcotic or alcohol abuse
7. Evidence of amputations (including toes), open ulcers, or Charcot joint.
8. Presence of other painful conditions.

BPI-sf (pain intensity and pain related interference with social activities) were applied to evaluate the effectiveness and safety of oxcarbazepine after the diagnosing diabetic neuropathy with Michigan Neuropathy Screening Instrument.[14,15] Michigan Diabetic neuropathy score screens patients using a simple questionnaire composed of questions about symptoms (such as pain, cramp, paresthesia and dysesthesia complaints) and physical findings (appearance of extremities, ulcer formation, reflexes and perception of vibration) and clinical assessment and those scoring in the abnormal range are then further assessed by detailed neurological examination and electrophysiological studies.[14] The BPI-sf is based on rating pain severity with visual analog scale in four categories (worst, least, average and right now) and pain-related interference in seven functional categories (general activity, mood, walking ability, work, relations with others, sleep, enjoyment of life).

BPI-sf was scored before initiating the treatment and at the end of the treatment in order to evaluate the efficacy of the treatment. Patients were also graded according to the change in pain and social subitems of BPI-sf as none if change was between 0-25% as minimal, 25-50% as mild, 50-75% as moderate and, more than 75% as extreme. Improvement was considered as a reduction of 50% or greater from the baseline in the pain intensity or social interference of BPI-sf subitems.

Patients received oxcarbazepine tablets 150 mg/day initially. Dosages were titrated up to 1200 mg, according to the tolerance of patients. Patients were requested to visit the clinic in a week and to titrate to the drug dosage up to 1200 mg. Patients were called and asked to continue their treatments and report or visit clinic if any adverse effects appear during the study.

In statistical analysis, Student’s t test and Mann-Whitney U tests were used to compare continuous variables. The Chi square test and Mann-Whitney Rank sum test were used for non-continuous data. The level of statistical significance was chosen to be P<0.05.

Results

This study group consisted of selected consecutive forty-three patients diagnosed with painful distal sensory-motor diabetic neuropathy (34 female and 9 male) based on clinical and electrophysiological examinations. Three patients were excluded because of not suitable for the follow-up and two patients discontinued during the study at the titration period. Thirty of thirty-eight patients were female and eight male. Patients were aged between 33 years and 62 years (mean 53.4±8.2 years).

None of these patients was receiving any drugs for their neuropathic symptoms prior to screening visit. Patients were requested not to use any of analgesics or other drugs for their neuropathic symptoms, but if so, record it and call the center. We did not have any patients receiving any drugs other that oxcarbazepine for the neuropathic symptoms.

There was not any significant difference in clinical laboratory tests (hematology, blood chemistries including electrolytes, glucose, lipid profile, liver, renal and function test results, total glycosylated hemoglobin and urinalysis) between the baseline and the final visit at the sixth month.

The changes in sub-items of BPI-sf and electrophysiological studies before initiating oxcarbazepine and at the end of the sixth month were shown in the Figures 1-2 and Table 1. Based on the scores achieved before initiating the treatment and at the end of the sixth month of treatment, there was a significant change in the scores of pain intensity and social interference of BPI-sf subitems (P<0.001) [Figures 1-2].

In BPI-sf pain intensity subitems, mean worst pain intensity score was 7.6±1.1 and 4.2±1.4 and least pain intensity score 3.9±0.9 and 1.9±0.9, average pain intensity score 6.3±0.9 and 3.2±0.9 and pain right now score was 5.7±1.2 and 2.8 ±1.1 at baseline and sixth month, respectively (P<0.001).

According to grading the changes in subitems of BPI-sf, of 38 patients, 59% had a 50% or greater decrease in pain intensity subitems [Table 1]. At the end of six months, improvement in pain intensity was observed in 52.7%, 63.1%, 55.3% and 63.2% of patients for the subitems of worst, least, average and pain now,
Figure 1: Change in the mean scores of BPI-sf pain intensity subitems before and after treatment of painful diabetic neuropathy patients. There was a significant difference between baseline and end-of-study scores in all pain subitems (P< 0.001).

Moreover, social interference had been improved in 62% of patients [Table 1]. Only 11% and 10.5% of patients were in the no or minor change group for the pain intensity and social interference, respectively. Improvement in social interference subitems was observed as 60.6, 63.2, 52.6, 60.5, 68.4 and 63.2% for subitems of general activity, mood, walk, work, people relations, sleep and life enjoyment, respectively.

The mean dose of oxcarbazepine was 1089.5±146.6 (Median dosage: 1200 mg). Twelve patients were observed to have side effects due to treatment. The most frequent side effect was dizziness (7 patients), followed by nausea (5 patients) and profound sleepiness (1 patient). None of these patients had hyponatremia or any prominent side effect leading to discontinue the treatment.

**Discussion**

Anticonvulsant drugs have been widely used in the treatment of neuropathic pain reasoning the fundamental mechanisms are similar with some epilepsy and neuropathic pain models, though their action is still limited understood. Anticonvulsants depress abnormal neuronal discharges and raise the threshold for neural impulse propagation. Long-term use of carbamazepine is limited due to side effects in such cases. Although it has been reported that valproic acid has no effect on pain in polyneuropathy, there have been recent studies reporting the efficacy of new antiepileptics such as pregabalin, lamotrigine and gabapentin on diabetic patients.

Increasing evidence suggests that oxcarbazepine can provide significant analgesia in several neuropathic pain conditions, including trigeminal neuralgia and PDN and is also effective in treating neuropathic pain refractory to other AEDs, such as carbamazepine and gabapentin. Thus, we aimed to investigate long-term efficacy and safety of oxcarbazepine in painful diabetic neuropathy.

Oxcarbazepine, an anti-epileptic, a keto-analog of carbamazepine, was shown to be effective in reducing pain in animal model. It has been reported that oxcarbazepine acts on inhibiting sustained, high frequency voltage-gated sodium channels merged with the

| Table 1: The distribution of the patients according to grading of change in pain intensity and social interference subitems of BPI-sf at baseline and the sixth month of the treatment (n: 38) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Grading BPI-sf  | No change or minor (0-25) | Mild change (25-50%) | Moderate change (50-75%) | Extreme (> 75%) |
| Pain intensity  | Worst pain       | 10.5             | 36.8             | 47.4             | 5.3             |
| Least           | 5.3              | 31.6             | 52.6             | 7.9              |                 |
| Average         | 5.3              | 39.5             | 47.4             | 15.8             |                 |
| Pain right now  | 5.3              | 31.6             | 47.4             | 15.8             |                 |
| Social interference | General activity | 7.9              | 31.6             | 55.3             | 5.3             |
| Mood            | 7.9              | 28.9             | 57.9             | 5.3              |                 |
| Walk or move    | 21.1             | 26.3             | 44.7             | 7.9              |                 |
| Normal work     | 10.5             | 28.9             | 52.6             | 7.9              |                 |
| People relations| 5.3              | 26.3             | 36.8             | 31.6             |                 |
| Sleep           | 15.8             | 21.1             | 55.3             | 7.9              |                 |
| Life enjoyment  | 10.5             | 21.1             | 57.9             | 10.5             |                 |
high voltage P/Q N-type calcium channels. 

The effectiveness of oxcarbazepine in treating neuropathic pain is probably due to its dual mode of action, which differentiates oxcarbazepine from other AEDs.

In our study, we had used BPI-sf comprising pain intensity and social interference (general activity, mood, walk, work, people relations, sleep and life enjoyment) subitems. A significant change in pain intensity and social interference subitems of BPI-sf was observed in diabetic neuropathic patients at the end of 6 months of the treatment (P < 0.01) [Figures 1-2]. According to grading the changes in subitems of BPI-sf, 58.6 and 62.4% of thirty-eight patient had a 50% or greater decrease, as a term of improvement, in pain intensity and social interference subitems, respectively [Table 1].

Although there have been a few clinical studies showing that oxcarbazepine is effective in neuropathic pain such as trigeminal neuralgia and post-herpetic neuralgia, Beydoun et al. reported that oxcarbazepine was effective in reducing the mean visual analog scale score about 48% in thirty diabetic neuropathy patients. In Beydoun’s study, although seven of the eight health concepts of Medical Outcomes Study Short Form 36 had been improved, only the bodily pain was reported to be improved statistically. Recently, Dogra et al. demonstrated in a randomized, multicenter, double-blind, placebo-controlled trial that OXC was effective in the treatment of painful diabetic neuropathy. It was reported that the results of the study showed that OXC significantly reduced pain severity from VAS scores (P = 0.01), more rapid onset of pain relief (P = 0.02, 22.5 versus 30.7 d), improvement (P = 0.0025, 48% versus 22%) and lower proportion of nights with awakening because of pain versus placebo (31% vs 49%, P = 0.02). The results of our study were similar with these two studies showing that oxcarbazepine had improved the quality of life significantly in patients with painful diabetic neuropathy. The effect on the life style of sufferers can be devastating, with loss of functions, social and workdays, quality of life should be inquired besides pain in order to evaluate the effectiveness of the treatment.

The recommended anticonvulsant dose of oxcarbazepine is 900-1200 mg/day. Therefore, in this study, oxcarbazepine with a dosage of 150 mg/day was initiated and titrated every other day up to 1200 mg. The dosage of and titration of oxcarbazepine was similar with the other study and the side effects were transient and mild. The most frequent side effect was dizziness and nausea. However, both our and Beydoun et al.’s studies had a limited number of patients a significant effect may also be achieved in a larger group of patients. The other side effects of oxcarbazepine are sedation, headache, dizziness, rash, vertigo, ataxia, nausea, diplopia and hypotension. The frequency of hypotension with oxcarbazepine has been reported to range from 22 to 73%. There is no significant serum Na level change at the end of our study.

Limitations of the study included, no control group was taken and could not study placebo effect on parameters. In Beydoun et al.’s study, it was shown that the effect of oxcarbazepine was almost stable after fifth week, at the end of titration phase. In our study, we did not evaluate the start of effectiveness or the change in week, since our main aim was to evaluate the effectiveness in the long-term use of oxcarbazepine.

To our knowledge, there is not any study for evaluating the long-term effectiveness of oxcarbazepine in diabetic neuropathic patients. In this study, oxcarbazepine was found to be effective and safe in long-term symptomatic treatment of painful diabetic neuropathy.

References

Diabetic peripheral neuropathy is a common complication of diabetes that can cause functional disturbance and clinical morbidity. It is usually characterized by an insidious onset and symmetrical distribution. Sensory features of reduced or absent sensation and altered or painful sensation are present. Mechanisms that may lead to the development of diabetic neuropathy include oxidative stress, sorbitol accumulation (advanced glycation end products), polyol pathway flux and protein kinase C. All these contribute to microvascular disease and nerve dysfunction. Hyperglycemia is considered to be the primary risk factor for diabetic neuropathy which emphasizes the importance of good glycemic control in preventing the development of diabetic neuropathy.

The attempts to treat diabetic neuropathy by manipulating the underlying metabolic pathways have not produced significant symptomatic relief. Symptomatic treatment is generally the only useful measure. Pain relief has been achieved by different medications including tricyclic drugs, different anticonvulsants, tramadol, meptxetine or capsaicin used in topical ointments. Increasing experience has been gained. Also non-steroidal anti-inflammatory drugs, opioid analgesics and new anti-depressant drugs have been used as adjuvant agents.

In recent years, several new-generation antiepileptic drugs such as gabapentin and pregabalin have been introduced in clinical practice and they have been shown to be quite effective and well tolerated in the treatment of diabetic neuropathy. New approaches to therapy are still needed, because many patients do not achieve good enough pain relief or they suffer side effects preventing the long term use of the previous drugs. Oxcarbazepine is a second-generation antiepileptic drug, which has been shown to be effective in managing partial epileptic seizures. It has also been shown to have fewer side effects than carbamazepine. Animal studies and two human studies have suggested that oxcarbazepine monotherapy may be efficacious and may provide clinically meaningful pain relief in diabetic patients with neuropathic pain.

The results of the study published at this journal also shows that oxcarbazepine administered as monotherapy is an efficacious and safe option for the symptomatic treatment of pain associated with symmetrical diabetic neuropathy. Moreover, social interference including general activity, mood, walk, work, people relations, sleep and life enjoyment were improved by the use of oxcarbazepine. None of the patients had prominent side effects. Although these results will need to be confirmed in double-blind, placebo-controlled, randomized clinical trials, oxcarbazepine seems to be very promising new symptomatic treatment for diabetic neuropathy.

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References