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Original Research Article

A Hospital Based Randomized Clinical Assessment of the Effect of Pregabalin in Patients with Neuropathic Pain

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Abstract

Aim: To evaluate the efficacy of pregabalin in the treatment of painful diabetic neuropathy.

Materials and Methods: The present study was conducted in the Department of General Medicine, Jannayak Karpoori Thakur Medical College and Hospital Madhepura,, Bihar, India for 10months, and twenty patients were recruited with diabetes and painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years were potentially eligible to enter into the study.

Results: Efficacy results indicate that pregabalin 600 mg/day significantly decreased mean pain score to 4.3 (vs 5.6 for placebo, P _ .0002) and increased the proportion of patients who had a >50% decrease from baseline pain (39% vs 15% for placebo, P _ .002). Pregabalin also significantly reduced sleep interference, past week and present pain intensity, sensory and affective pain scores, and bodily pain and decreased by >50% the number of patients describing their pain as gnawing, sickening, fearful, and punishing–cruel. More patients receiving pregabalin 600 mg/day than placebo showed improvement, as rated on the Clinical and Patient Global Impression of Change scales, 73% vs 45% and 85% vs 47%, respectively. Pregabalin 150 mg/day was essentially no different from placebo. Dizziness was the most common side effect.

Conclusion: These study results show pregabalin 600 mg/day to be safe and effective in reducing the pain and other associated symptoms of painful diabetic neuropathy.

Introduction

Neuropathic pain as defined by The International Association for the Study of Pain is “pain initiated or caused by a primary lesion in the nervous system”. In other words, neuropathic pain may be defined as the pain originated from the pathology of the nervous system. It involves alterations in the function, chemistry and structure of neurons. Spontaneous pain, hyperalgesia and allodynia are the common symptoms observed in neuropathic pain. Spontaneous pain is characteristically burning or shooting in nature. Hyperalgesia is an increased pain response to supra-threshold noxious stimulus, while allodynia is a sensation pain elicited by a non -noxious stimulus (e.g. the gentle touch of clothes, bending of cutaneous hairs by a puff of wind). Spontaneous pain may be simply conceptualized as “stimulus independent” whereas hyperalgesia and allodynia as “stimulus dependent”.

Neuropathic pain is a result of various mechanisms operating at the peripheral, spinal cord and supra-spinal levels, which cause alterations in the pain conduction pathway. This may also develop secondary to some other pathological conditions such as diabetes mellitus, cancer, herpes infection, autoimmune diseases and HIV infection etc. [1]

Pregabalin, (S)-3-(aminomethyl)-5-methylhexanoic acid, is a pharmacologically active S-enantiomer of a racemic 3- isobutyl gamma amino butyric acid analogue. It is well established anticonvulsant and analgesic agent. In fact pregabalin is the first drug to receive an approved labeling from Food and Drug Association (FDA) for the treatment of diabetic neuropathy and post-herpetic neuralgia. [2]

Preclinical and clinical studies have shown the effectiveness of pregabalin in managing the neuropathic pain. Animal based studies have helped to describe the mechanisms for its anti-hyperalgesia and anti-allodynic action. Clinical studies have also shown the efficacy and dose dependent effects of pregabalin either as monotherapy or in combination with analgesics in relieving pain and related symptoms. [3,4]

The major advantage of pregabalin is its relative reliability, easy use and high tolerance in patients with neuropathic pain. [5] As a successor of gabapentin, pregabalin has been shown to be effective in several models of neuropathic pain, incisional injury and inflammatory injury.

Gabapentin and pregabalin are often recommended for the treatment of NeP. [6,7-9] Both agents share the same mechanism of action, with their analgesic effects attributed to binding of the $\alpha_2\beta$ subunit of neuronal voltage-gated calcium channels and subsequent modulation of neurotransmitter release. [10] Studies with pregabalin suggest its analgesic effects may be mediated by reducing hyperexcitation in ascending pain pathways, reducing dysregulation in areas of brain associated with pain perception and modulation, and restoring inhibitory descending pain pathways. [11,12]

In this study, pregabalin was compared to placebo for its effect on pain and a variety of associated symptoms that commonly accompany diabetic neuropathy.

Materials and Methods

The present study was conducted in the Department of General Medicine, Jannayak Karpoori Thakur Medical College and Hospital Madhepura,, Bihar, India for 10 months, and twenty patients were recruited with diabetes and painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years were potentially eligible to enter into the study.

Neuropathy was confirmed by history and detailed neurologic examination. Inclusion criteria included age 18 years, hemoglobin A1C levels _11%, and the ongoing experience of moderate to severe pain. Exclusion criteria included neurologic disorders unrelated to diabetic neuropathy, any condition that could confound study assessments, recent treatment with any investigational drug, or serious medical problems. Women could not be lactating and were required to have a negative pregnancy test result and to use appropriate contraception if of childbearing potential.

Eligible patients had to meet additional criteria for poorly controlled pain, including a score of 40 mm on the visual analog scale (VAS) of the Short Form-McGill Pain Questionnaire[13] (SF-MPQ) and an average daily pain score 4 for 4 or more days during baseline. Phenothiazines, antiarrhythmic agents, and pteridine and the combination of antihistamines and macrolide antibiotics were prohibited during the study owing to their proarrhythmic activity. Other medications that could affect efficacy or safety were to be discontinued either 14 days (antiepileptic drugs, nonsteroidal anti-inflammatory drugs) or 30 days (opioids, tricyclic antidepressants, benzodiazepines, muscle relaxants, capsaicin, mexiletine, dextromethorphan) before being administered study drug. Aspirin (for prophylaxis of myocardial infarction and transient ischemic attacks), acetaminophen (3 g/day), and stable doses of serotonin reuptake inhibitors were allowed.

Patients were randomly assigned to pregabalin (150 or 600 mg/day) or placebo. After a 1-week baseline, eligible patients entered a 6-week (2-week titration/4-week fixed dose) double-blind treatment phase. The dose of pregabalin was titrated from 25 mg/day to 150 mg/day or from 100 mg/ day to 600 mg/day during the 2-week titration period and fixed thereafter. Pregabalin was provided as 2 differently sized capsules. To assure blinding, study medication was provided in 2 bottles, one with small-sized capsules containing 25 mg pregabalin or placebo and the other with large-sized capsules containing 100 mg pregabalin or placebo. Patients took 2 capsules from each bottle 3 times daily. At each stage of the study, including titration, all patients, regardless of treatment group, took the same number of capsules from each bottle per day. The blind was maintained until completion of study and data evaluability determination. Visits occurred at the start of baseline (week –1) and double-blind phases (week 0) and then biweekly (weeks 2, 4, and 6).

The primary efficacy parameter was pain. Each day on awakening, patients recorded their pain during the previous 24-hour period by circling the appropriate number on a numeric scale of 0 (no pain) to 10 (worst possible pain) in a daily diary. Secondary efficacy parameters assessed pain characteristics, sleep interference, health status, psychologic state, and global improvement. The SF-MPQ[13] a well-validated multidimensional pain questionnaire, recorded past week pain intensity on a VAS ranging from 0 mm (no pain) to 100 mm (worst possible pain), present pain intensity (PPI) on a numeric scale of 0 (none) to 5 (excruciating), and past-week intensity of each of 11 sensory and 4 affective descriptors of pain on a numeric scale from 0 (none) to 3 (severe). The latter were summed to yield sensory and affective scores and added for total score. Sleep interference was recorded in daily diaries on a numeric scale of 0 (did not interfere with sleep) to 10 (completely interfered, unable to sleep because of pain). Clinician and Patient Global Impression of Change (CGIC, PGIC) were each scored from 1 (very much improved) to 7 (very much worse) at the final visit.

Safety was evaluated by adverse events (AEs); clinical laboratory determinations; electrocard iogram; and general medical, neurologic, and ophthalmologic examinations.

The neurologic examination included a clinician rated question assessing the presence or absence of allodynia. Changes from baseline to the end of the double- blind phase in examination data were

recorded as AEs if they were deemed clinically significant by the investigators. Plasma pregabalin concentrations from blood collected at weeks 0, 2, 4, and 6 were determined by using a validated high-performance liquid chromatographic method with ultraviolet detection. Predicted (based on a pharmacokinetic model of pregabalin constructed from data rich [serial plasma collections] single- and multiple dose studies in healthy volunteers, including a single dose tolerance and pharmacokinetic study, 2 multiple dose tolerance and pharmacokinetic studies, and a

single-dose, food-effects study) versus observed pharmacokinetic values were analyzed by using nonlinear mixed effects modeling (NONMEM Version V; University of California at San Francisco, San Francisco, Calif).

Analyses were conducted on the intent-to-treat population (all randomized patients who received at least one dose of study medication). Analysis of covariance main effects models, with baseline as covariate and 95% confidence intervals (CIs), were constructed on the difference in least square (LS) means between each of the two dosages of pregabalin and placebo to evaluate group differences in pain scores from daily pain diaries, SF-MPQ scores, sleep interference scores, POMS scales, and scores on the SF-36 domains.

Results

Demographic and baseline characteristics are summarized in Table 1.

At end point, patients receiving 600 mg/day pregabalin had a significantly lower mean pain score than did patients receiving placebo (*P* _ .0002) (Table 2), and significantly more had a _50% reduction from baseline pain (*P* _ .002) (Fig 2). Starting at week 2, when they were receiving the full 600 mg/day dosage of pregabalin, these patients had significantly greater weekly decreases from baseline mean pain scores (*P* <.05 vs placebo).

VAS, PPI, sensory, affective, and total scores on the SF-MPQ were all significantly lower after treatment with 600 mg/day pregabalin (*P*_.01 vs placebo) (Table 3). The percentage of patients who reported gnawing, sickening, fearful, and punishing-cruel pain was more than halved. Decreases from baseline VAS, PPI, and total scores were greater starting at week 2, the first assessment of these parameters during the treatment phase (*P* <.05 vs placebo).

There were no treatment-related differences in mood assessed by the POMS or in health status assessed by the SF-36, except for bodily pain, which was significantly improved by both doses of pregabalin (*P* _ .0106 for either dose vs placebo). Pregabalin 150 mg/day was not significantly different from placebo on any other efficacy parameter.

There were no clinically significant changes in deep tendon reflexes or peripheral sensory examination (pin prick, vibration perception) among treatment groups, but among patients with allodynia at baseline, most no longer reported allodynia after pregabalin (18/28 [64.3%] 600-mg/day and 13/23 [56.5%] 150-mg/day vs 5/22 [22.7%] placebo).

A summary of treatment-associated and not-associated AEs by decreasing frequency appears in Table 4. The most common treatment-associated AEs in the 600-mg/ day group were dizziness (30.5% of patients), somnolence (18.3% of patients), and headache (13.4%), whereas in the 150-mg/day group, the most common AEs were dizziness (6.3%), somnolence (5.1%), and asthenia (3.8%). In the placebo group, headache (7.1%) and somnolence, asthenia, and amblyopia (3.5% each) were the most commonly observed treatment-associated AEs.

Most AEs were of a maximum intensity of mild or moderate. AEs considered severe that occurred in more than

1 patient in the 600-mg/day group were dizziness (3 patients), somnolence (2 patients), and asthenia (2 patients).

No AEs considered severe were reported by more than 1 patient in the 150-mg/day pregabalin group. Together, dizziness, somnolence, and headache caused 9 patients to discontinue the study (6 pregabalin 600-mg/ day, 1 pregabalin 150-mg/day, 2 placebo). There were no clinically significant differences among treatment groups in ophthalmologic examinations, physical examination parameters, including orthostatic hypotension and electrocardiogram, and no evidence of worsening glucose control or diabetic ketoacidosis.

Table 1. Baseline Demographic and Disease Characteristics

CHARACTERISTIC	PLACEBO (n=10)	Pregabalin	
		150 MG/DAY (n=5)	600 MG/DAY (n=5)
Men/women	10	5	5
Age (y), mean _ SD	57.1 ± 10.3	56.3 ± 9.4	57.8 ± 9.5
Weight (kg), mean _ SD	90.81 ± 20.40	97.96 ± 18.37	96.55 ± 19.77
Diabetes characteristics			
Type 1, N	5	3	3
Type 2, N	5	2	2

HbA1c values, mean _ SD	8.1 ± 1.4	8.2 ±1.5	8.2 ± 1.4
Duration (y), mean _ SD	10.6 ± 8.3	8.2 ± 9.1	9.3 ± 8.8

Table 2: Short-Form McGill Pain Questionnaire Scores

SCORE	TREATMENT	Mean±SD	P VALUE
VAS	Placebo Pregabalin 150 mg/day 600 mg/day	58.05 ± 2.68 53.27 ± 2.75 43.38 ± 2.70	.2058 .0002
PPI	Placebo Pregabalin 150 mg/day 600 mg/day	1.96 ±0.11 1.78 ± 0.12 1.30 ±0.12	.2836 .0002
Sensory	Placebo Pregabalin 150 mg/day 600 mg/day	14.61 ± 0.73 12.65 ±0.76 10.07 ± 0.74	.0570 .0002
Affective	Placebo Pregabalin 150 mg/day 600 mg/day	3.35 ±0.29 2.78 ± 0.30 2.04 ± 0.30	.1664 .0028
Total	Placebo Pregabalin 150 mg/day 600 mg/day	17.97 ±0.96 15.48 ± 0.99 12.14 ± 0.97	.0651 .0002

Table 3: Adverse Events

PREGABALIN			
ADVERSE EVENT	PLACEBO	150 MG/DAY	150 MG/DAY
Dizziness	2.4	10.1	37.8
Somnolence	3.5	5.1	22.0
Peripheral edema	4.7	3.8	17.1
Headache	10.6	7.6	15.9
Asthenia	3.5	3.8	12.2
Accidental injury	5.9	2.5	9.8
Weight gain	0	1.3	9.8
Amblyopia	5.9	2.5	8.5
Dry mouth	2.4	0	8.5
Pain	8.2	3.8	7.3
Constipation	4. 7	3.8	6.1
Infection	9.4	12.7	6.1
Diarrhea	3.5	5.1	2.4

Discussion

Painful neuropathy is highly prevalent in the diabetic population and can profoundly undermine quality of life. [14] Pain management is an essential component in the comprehensive care of these patients. Several controlled studies have demonstrated that painful diabetic peripheral neuropathy can be relieved by antidepressants19 anticonvulsants [10] tramadol [15] agonist opioids [16] and topical application of capsaicin,29 and recent meta-analyses [17,15] support those findings. Unfortunately, the use of these agents can be limited by the extent of pain relief provided and the occurrence of significant side effects. Thus, a need exists for additional safe and effective agents for painful diabetic peripheral neuropathy.

In this study, patients who received pregabalin 600 mg/day experienced significantly less pain than those who received placebo. The average reduction in pain score from baseline was 2.4 on a 0 to 10 numeric scale, with 39% of patients having 50% reduction in their pain. This degree of response is widely considered to be clinically meaningful and corresponds with the highest degree of improvement

assessed by PGIC. [18,19] Treatment with pregabalin at 600 mg/day also reduced sleep interference and significantly improved all components of the SF-MPQ by week 2. A lower prevalence of allodynia, improvement in bodily pain, and substantial global improvement were observed at study's end. Pregabalin showed predictable pharmacokinetics and was well tolerated, as evidenced by the low rates of study discontinuation.

Although direct comparisons of pregabalin with tricyclic antidepressants and gabapentin have not been conducted, the findings in this study suggest that pregabalin produces clinically significant improvement in the range observed with these other drugs. Pregabalin is structurally and mechanistically related to gabapentin but differs from gabapentin in exhibiting linear pharmacokinetics with increasing dose and low intersubject variability. These properties might make pregabalin easier to prescribe and might impart a better-defined effective dose range.

In another controlled trial, pregabalin 300 mg/day also significantly improved pain, sleep interference, and mood in patients with painful diabetic neuropathy.23 Together, these 2 independent, randomized clinical trials constitute evidence that pregabalin at 300 or 600 mg/day produces significant improvement of pain, sleep, and at least some aspects of health status and mood. Consistent with clinically recognized, dose-dependent effects of anticonvulsants in neuropathic pain, best characterized with gabapentin, 1 pregabalin 150 mg/day did not differ from placebo.

Despite substantial advances in pharmacotherapy of neuropathic pain, outcomes are often unsatisfactory.

Many drugs are tried despite a lack of evidence for safety or efficacy in the diabetic population, emphasizing the need for controlled clinical trials of new pharmacother-apies to expand treatment options and further the goal of evidence-based decision making. The present, 6-week study establishes that pregabalin 600 mg/day is safe and effective in patients with painful diabetic neuropathy.

Although no conclusions about the durability of response or AE profile during long-term administration can be drawn from this study, 75 patients (91%) treated with 600 mg/day pregabalin and 73 patients (92%) treated with pregabalin 150 mg/day entered the open label extension, and 73 patients (86%) treated with placebo were converted to pregabalin treatment for the open-label extension. Additional studies are needed to further explore dose response at higher doses, provide comparative efficacy data against other treatments, assess value of combination therapies, and confirm long-term treatment effectiveness.

Conclusion

Overall, the findings indicated that pregabalin may be used successfully to treat patients with NeP who may be refractory, respond inadequately, or are intolerant to gabapentin. However, further controlled studies that more completely document patients' previous response to gabapentin would add additional support to our conclusions. In a broader sense, our findings highlight the importance of tailoring treatment of NeP based on individual patient response to different treatments, including the trial of multiple agents within the same mechanistic class.

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