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Efficacy and Tolerability of a Fixed Dose Combination of Pregabalin and Nortriptyline in the Management of Diabetic Peripheral Neuropathy among Indian Population

Research Article

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Abstract

Background: Treatment of Diabetic Peripheral Neuropathy (DPN) is challenging, and effective therapies are not available for many patients; therefore, developing improved pharmacotherapy is essential. A combination therapy of pregabalin with nortriptyline could provide enhancing and complementary effects through different mechanism of action, thereby reducing the symptoms. However, there are only limited studies available to support this combination.

Objective: To assess the safety and tolerability of a fixed dose combination of pregabalin and nortriptyline in the treatment of diabetic peripheral neuropathy among Indian population.

Methods: This was a multi-centric, open label, observational, phase IV (post-marketing surveillance) study conducted among type 2 diabetes mellitus patients with the evidence of painful diabetic neuropathy over last 1 month with the mean pain intensity of more than 50% by patient assessment by NRS (numerical rating scale). The enrolled subjects received the fixed dose combination of Pregabalin 75 mg and Nortriptyline 10 mg once daily in the morning. Efficacy was evaluated by measuring the change in the mean pain score (on the 11-point NRS) derived from entries on patient visits on visit 1 (baseline visit; day 1), to visit 3 (day 28). Efficacy was further evaluating using the Patient Global Impression of Change (PGIC) and Daily Sleep Interference Rating Scale (DSIRS). Safety was assessed by evaluating the nature, duration, severity, and causal relationship of all adverse events to the study drug which were documented at each clinic visit.

Results: Out of 224 subjects screened, 210 subjects were enrolled who had at least one visit and were administered at least one dose of the study medication. The mean pain score measured on the Numerical Rating Scale (NRS), Daily Sleep Interference Rating Scale (DSIRS) and Patient Global Impression of Change (PGIC) scale during visit 1/ baseline visit was 7.94, 7.00 and 4.00 which was reduced on visit 2 and further decreased into 2.46, 3.48 and 1.39 on visit 3 respectively.A total of 12 subjects (6%) reported adverse events and were mild in severity and completely resolved within 24 hours of administering symptomatic/ appropriate medications.

Conclusion: The fixed dose combination of Pregabalin and Nortriptyline was efficacious and well-tolerated in the therapeutic management of patients with diabetic peripheral neuropathy.

Keywords: Diabetic peripheral neuropathy; Pregabalin; Nortriptyline; Diabetes mellitus; Neuropathic pain

Introduction

Diabetes mellitus (DM) is a chronic metabolic condition characterised by hyperglycemia as a primary symptom whereas chronic hyperglycemia leads to long-term damage and dysfunction to multiple tissues and organs (such as the eyes, kidneys, nerves, heart, and blood vessels) [1]. Diabetic peripheral neuropathy (DPN) is described as "a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and micro vascular alterations as a result of prolonged hyperglycemia and cardiovascular comorbidities" by the Toronto Consensus Panel on Diabetic Neuropathy. Sensory complaints typically manifest initially in the toes and progress to the upper limbs in a "stocking and glove" pattern. In the first phases of DPN, motor participation is not frequently observed. Patients describe a variety of sensory symptoms, including allodynia (painful sensation to innocuous stimuli) or hyperalgesia (increased sensitivity to painful stimuli), loss of pain sensation or "Novocain-like" insensitivity, tingling, "pins and needles" sensation, burning, and "electric shocks" [2].

The development of more effective therapy is crucial since treating DPN is difficult and many patients do not have access to appropriate therapies. There is a dearth of information on pharmaceutical and combination therapies that can stop or reverse DPN alterations or partially relieve pain and thus, the therapeutic management of painful DPN has a variety of unmet requirements [3].

Currently, Pregabalin, a GABAergic drug that is primarily used as a first-line agent to treat painful DPN. As well as providing adequate pain relief, it was well tolerated and the co-morbidities of DPN, such as anxiety and sleep issues, can also be effectively treated with it [4-6]. Another molecule, nortriptyline, a tricyclic antidepressant and the primary active metabolite of amitriptyline has modest antimuscarinic effects and has been demonstrated to be useful in treating diabetic peripheral neuropathy by inhibiting the reuptake of norepinephrine and serotonin [7-9]. A combination therapy of pregabalin with nortriptyline could provide enhancing and complementary effects through different mechanism, thereby reducing the symptoms [10, 11]. However, there are only limited studies available characterizing the efficacy and safety of combination therapy of pregabalin and nortriptyline, particularly in the management of diabetic peripheral neuropathy on the Indian population. Hence, this study was designed to assess the efficacyand tolerability of pregabalin with nortriptyline as treatment for diabetic peripheral neuropathy.

Methods

A multi-centric, open label, observational, phase IV (post-marketing surveillance) study conducted to assess the safety and efficacy of combination of Pregabalin and Nortriptyline in diabetic peripheral neuropathy. This study included patients who were either on an inpatient or outpatient basis with the presence of type 2 diabetes mellitus and the evidence of painful diabetic neuropathy over last 1 month with the mean pain intensity of more than 50% by patient assessment by NRS (numerical rating scale). Subjects having intolerance, hypersensitivity or any other contraindication to either Pregabalin or Nortriptyline, evidence of other causes for neuropathy and painful conditions, pregnant and lactating subjects were excluded from the study. The enrolled subjects received the fixed dose combination of Pregabalin 75 mg and Nortriptyline 10 mg once daily in the morning.

Efficacy was evaluated by measuring the change in the mean pain score (on the 11-point NRS) derived from entries on patient visits on Visit 1 (Baseline Visit; Day 1), Visit 2 (Day 14) and Visit 3 (Day 28) where the numeric rating scale ranged from 0 being no pain to 10 being the worst possible pain. A rating of 1-3 was considered as mild pain, 4-6 as moderate pain, and 7-10 as severe pain. Efficacy was further evaluated using the Patient Global Impression of Change (PGIC) and Daily Sleep Interference Rating Scale (DSIRS). Safety was assessed by evaluating the nature, duration, severity, and causal relationship of all adverse events to the study drug which were documented at each clinic visit.

Statistical analysis was done by using SPSS (Statistical Package for Social Sciences) of version 27 and R software. To test the hypotheses of the study, descriptive statistics (mean and SD) and inferential statistics, Friedman's ANOVA (analysis of variance) test were used. Value of $P<0.001$ were considered significant.

Results

A total of 224 subjects were screened from all participating study centers on visit 1 (day 1), which included physical examination, vital signs including height, weight and blood pressure, and assessment of pain on the Numerical Rating Scale (NRS).Out of 224 subjects, 210 subjects were enrolled after meeting the inclusion and exclusion criteria during the screening and 14 subjects were found not eligible for enrolment and were deemed to be screen failures. A total of 7 subjects dropped out or were lost to follow up on visit 2 and/or visit 3. The total number of subjects who completed all visits and were analysed for efficacy was 203. The total number of subjects who had at least one visit and were administered at least one dose of the study medication were analysed for safety was 210.

The mean score of pain on the Numerical Rating Scale (NRS) during visit 1/ baseline visit was 7.94 ± 0.62. The mean pain score subsequently decreased to 4.95 ± 0.78 on visit 2. The mean score further decreased to 2.46 ± 0.80 on visit 3 as depicted in [Figure 1]. The mean score observed on the Daily Sleep Interference Rating Scale (DSIRS) during visit 1/ baseline visit was 7.00 ± 1.05. The mean pain score subsequently decreased to 3.96 ± 1.11 on visit 2. The mean score further decreased to 3.48 ± 1.22 on visit 3 as shown in [Figure 2]. The mean score noted on the Patient Global Impression of Change (PGIC) scale during visit 1/ baseline visit was 4.00 ± 0.00. The mean pain score subsequently decreased to 1.63 ± 0.61 on visit 2. The mean

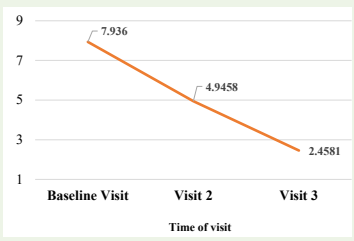

Figure 1: Mean Scores on Numerical Rating Scale

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score further decreased to 1.39 ± 0.58 on visit 3 [Figure 3]. These scores were found to be highly significant (p<0.001) on Friedman's ANOVA (analysis of variance) test with confidence interval of 95%.

The change in the mean pain score on the Numerical Rating Scale (NRS) from visit 2 to visit 1/ baseline visit was -2.99 ± 0.99. The change in the mean pain score from visit 3 to visit 2 was -2.49 ± 1.14. The change in the mean pain score on the Numerical Rating Scale (NRS) from visit 3 to visit 1/baseline visit was -5.48 ± 1.02.The change in the mean pain score on the Daily Sleep Interference Rating Scale (DSIRS) from visit 2 to visit 1/ baseline visit was -3.03 ± 1.58. The change in the mean pain score from visit 3 to visit 2 was -0.48 ± 0.50. The change in the mean pain score on the Daily Sleep Interference Rating Scale (DSIRS) from visit 3 to visit 1/ baseline visit was -3.52 ± 1.68. The change in the mean pain score on the Patient Global Impression of Change (PGIC) from visit 2 to visit 1/ baseline visit was -2.37 ± 0.61. The change in the mean pain score from visit 3 to visit 2 was -0.24 ± 0.45. The change in the mean pain score on the Patient Global Impression of Change (PGIC) from visit 3 to visit 1/ baseline visit was -2.61 ± 0.58. There was no worsening of pain as assessed by the Patient Global Impression of Change (PGIC) in any of the study subjects on visit 2 or visit 3. The change in scores were found to be significant (p<0.001) on Wilcoxon signed-rank test with confidence interval of 95% [Table 1].

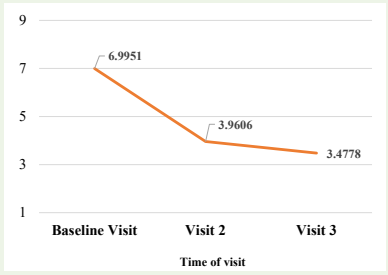

Figure 2: Mean Scores on Daily Sleep Interference Rating Scale.

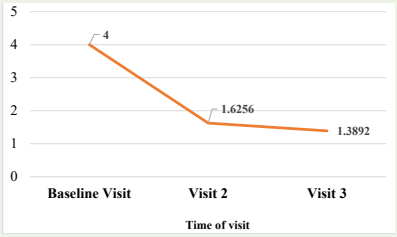

Figure 3: Mean Scores on Patient Global Impression of Change.

Table 1: Change in the efficacy parameters during each subject visit

Efficacy parameters	Change from Visit 2 to Visit 1/ Baseline visit	Change from Visit 3 to Visit 2	Change from Visit 3 to Visit 1/ Baseline visit	p value*
	Score ± SD			
NRS	-2.99 ± 0.99	-2.49 ± 1.14	-5.48 ± 1.02	<0.001
DSIRS	-3.03 ± 1.58	-0.48 ± 0.50	-3.52 ± 1.68	
PGIC	-2.37 ± 0.61	-0.24 ± 0.45	-2.61 ± 0.58	

*Friedman's ANOVA test with p value <0.05

A total of 12 subjects (6%) reported adverse events, of these 5 subjects each were from RIMS, Srikakulam and Shetty's Hospital, Bangalore; 3 subjects were from Medipoint Hospitals, Pune, and 2 subjects from GSVM, Kanpur. All 12 adverse events were unrelated to the investigational product and were mild in nature. All events resolved completely after the administration of appropriate medications, including over-the-counter medications. The most common adverse events reported were body pain with 3 subjects (1.5%) and headache and drowsiness with 3 subjects (1.5%). A total of 2 subjects each (0.5%) reported fever and pain, hyperacidity and fever respectively. All adverse events were mild in severity and completely resolved within 24 hours of administering symptomatic/ appropriate medications for the same.

Discussion

More than one-third of diabetic patients have diabetic neuropathy, a disorder that can lower their quality of life [12].Neuropathic pain, which affects 8 to 26% of diabetic patients, is also regarded as one of the most challenging pain syndromes to manage. Despite standard treatment approaches, fewer than 50% of patients experience relief, and the majority of patients still experience pain [13]. A few studies comparing the medications used to treat neuropathic pain have been carried out. This is the first study that directly compares pregabalin and nortriptyline.

The present study showed that the mean pain scores of the Numerical Rating Scale (NRS) decreased from 7.9360 ± 0.62207 on visit 1 to 4.9458 ± 0.78477 on visit 2 and to 2.4581 ± 0.79725 on visit 3, which was found to be statistically significant with p <0.05 with 95% confidence interval on Friedrich's ANOVA test. Comparison of the scores from visit 3 (end of the study) to the baseline visit also showed that the decrease in the pain score on the Numerical Rating Scales were statistically significant on the Wilcoxon Singed-Rank Test, Z= -12.572, p <0.05.In line with this, Khajuria et al. pointed out that there was a statistically significant decrease in post drug mean NRS scores with both pregabalin and nortriptyline group from baseline during entire 8 week's trial (p<0.0001) [14].

The findings of this study were similar to Shahid W et al. who reported a decrease in mean VAS score from 6.99 ± 1.12 to 4.91 ± 0.82 with 12 weeks of therapy with pregabalin (p <0.0001) [4]. Mahmood R et al. reported the mean pain score fell from 6.17 ± 0.14 to 3.50 ± 0.15 from day 0 to day 90 (p = 0.001) with pregabalin [15]. Bansal D et al. reported good, moderate and mild pain relief were noted in 21 (48%), 6 (13%) and 7 (15%) patients on pregabalin [16].Lesser H et al. highlighted that patients in the 300- and 600-mg/day pregabalin groups showed improvements in mean pain score (primary efficacy measure) compared to placebo (p = 0.0001). Improvements were also seen in weekly pain score, sleep interference score, patient global impression of change, clinical global impression of change, SF-McGill Pain Questionnaire, and multiple domains of the SF-36 Health Survey. Improvements in pain and sleep were seen as early as week 1 and were sustained throughout the 5 weeks [17]. Tölle T et al. reported that pregabalin 600 mg/day was significantly superior to placebo in improving pain-related sleep-interference scores (p = 0.003), PGIC (p = 0.021), and CGIC (p = 0.009) and all pregabalin

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dosages were superior to placebo in improving EQ-5D utility scores (all p >/= 0.0263 vs placebo) [18].Gomez-Perez FJ et al. in two separate studies demonstrated the efficacy of nortriptyline along with fluphenazine brought significant relief of both pain and paresthesia in subjects with painful diabetic neuropathy [19,20].

The mean scores of the Daily Sleep Interference Rating Scale (DSIRS) decreased from 6.9951 ± 1.05068 on visit 1 to 3.9606 ± 1.10732 on visit 2 and to 3.4778 ± 1.21999 on visit 3, which was found to be statistically significant with $p<0.05$ with 95% confidence interval on Friedrich's ANOVA test. Comparison of the scores from visit 3 (end of the study) to the baseline visit also showed that the decrease in the pain scores on the Numerical Rating Scales were statistically significant on the Wilcoxon Singed-Rank Test, Z= -12.191, $p<0.05$.

The mean scores of the Patient Global Impression of Change (PGIC) decreased from 4.00 ± 0.00 on visit 1 to 1.6256 ± 0.61155 on visit 2 and to 1.3892 ± 0.58129 on visit 3, which was found to be statistically significant with $p<0.05$ with 95% confidence interval on Friedrich's ANOVA test. Comparison of the scores from the end of the study to the baseline visit also showed that the decrease in the pain scores on the Numerical Rating Scales were statistically significant on the Wilcoxon Singed-Rank Test, Z= -12.807, $p<0.05$.

Safety and tolerability analysis revealed that a total of 12 subjects (6%) reported adverse events and the most common adverse events reported were body pain with 3 subjects (1.5%) and headache and drowsiness with 3 subjects (1.5%). Two subject each (0.5%) reported fever and pain, hyperacidity and fever respectively. Shahid W et al. reported that lethargy/ somnolence (8.1%) and peripheral edema (3.4%) were the commonly reported adverse events in the pregabalin group and that pregabalin was efficacious in the relief of neuropathic pain with good safety profile and was well tolerated [4]. Azmi S et al. also reported that the most frequent adverse events with pregabalin were somnolence and dizziness, which can lead to withdrawal in ~30% of long-term use [21]. In a study by Bansal D, it was observed that pregabalin caused adverse events in 18 (25%), of which drowsiness was the most common in nine (20%) patients [16]. Another study by Lesser H also reported that the most common adverse events were dizziness and somnolence with pregabalin [17]. Gomez-Perez FJ et al. reported that the adverse effects were not severe enough to lead to cessation of nortriptyline [19].

To the best of the authors knowledge, this was the first study assessed the fixed dose combination of Pregabalin with Nortriptyline among diabetic peripheral neuropathy patients in various centres. Although this study was conducted using robust methodology and stringent inclusion and exclusion criteria, certain limitations need to be considered while interpreting the results. The study had a small sample size and included sample of patients with a similar race and cultural background, and smaller duration of follow-up; thus, the generalizability of the results should be made with caution. So, it should be proved in a larger sample size with different race and ethnicity to provide more specific results.

Conclusion

The fixed dose combination of Pregabalin 75 mg and Nortriptyline 10 mg was efficacious and well-tolerated in the therapeutic management of patients with diabetic peripheral neuropathy.

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Conflict of interest: Manjula S and Krishna Kumar M are employees of Micro Labs Limited, India.

Ethical approval: This study was approved by Institutional Ethics Committee Government Medical college, Government General Hospital, Srikakilam; Life Care Hospital Institutional Review Board Life Care hospital and Research centre, Sahakarnagar, Bangalore; Institutional Ethics Committee of GSVM and Shetty's Hospital Ethics committee.

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