|| Print ISSN: 2589-7837 || Online ISSN: 2581-3935 ||

International Journal of Medical Science and Diagnosis Research (IJMSDR)

Available Online at www.ijmsdr.com

Volume 3, Issue 2; February: 2019; Page No. 25-30

STUDY OF SAFETY AND EFFICACY OF THE COMBINATION OF AMITRIPTYLINE AND PREGABALIN SR IN SEVERE NEUROPATHIC PAIN: DATA OF LOGIC TRIAL

Dr. Mayuresh Dilip Kiran[1], Lalit Jeevan Pawaskar[2], Shaheen Naseem Sheikh[3]

[1]Vice President, Medical Services, Centaur Pharmaceuticals Pvt. Ltd

[2]Executive, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd

[3]Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd

Conflicts of Interest: Nil

ABSTRACT:

Objective: To evaluate the safety and efficacy of the combination of amitriptyline and pregabalin SR in patients of severe neuropathic pain not controlled on monotherapy of a neuroanalgesic.

Methods: LOGIC Study was conducted at 120 centres on 1269 patients across India. Patients above 18 years with severe neuropathic pain not controlled on monotherapy of a neuroanalgesic and who satisfied the inclusion and exclusion criteria were enrolled in the study. A combination of amitriptyline and pregabalin SR was given once daily. Patients were evaluated for the efficacy by visual analogue scale (VAS). Safety was evaluated through the noting adverse events occurring during the study. Patients VAS score were noted at baseline(visit 1), day 7(visit 2), day 21(visit 3) and also asked for any adverse events. Change in mean VAS score, percentage of patients achieving ≥50% reduction in pain at every visit and Number Needed to Treat (NNT) was assessed.

Results: Mean VAS score was 7.87 at baseline, 5.6 at day 7 and 3.42 at day 21. 46.4% and 84.6% of total patients at day 7 and 21 respectively had a reduction in pain of ≥50% from the baseline. NNT was calculated to be 1.19 for achieving ≥50% pain relief. Reduction in pain intensity was irrespective of blood glucose control, age and gender of the patient. Adverse effects were observed in 15% patients of patients – Sedation, Dizziness, Dry Mouth and Constipation were predominant.

Conclusion: Combination of amitriptyline and pregabalin SR is safe and efficacious in the treatment of severe neuropathic pain.

Keywords: Amitriptyline, Pregabalin, Severe Neuropathic Pain, NNT.

Introduction

Pain is one of the most common complaint which brings a patient to the doctor. Neuropathic pain mainly occurs due to damage to the nerves and is characterized by absence of external painful stimulus. The International Association for the Study of Pain (IASP) defined Neuropathic pain as "pain resulting from damage or disease of the central or peripheral nervous systems, and from dysfunction of the nervous system".[1]

There are many causes of neuropathic pain like Diabetes, Neuritis, Radiculopathy, Spinal Cord Injury and Post-Herpatic Neuralgia.[1,3]

Diabetic peripheral neuropathy (DPN) is an important & advancing microvascular complication of diabetes mellitus.[4] According to an estimate; two thirds of diabetic patients have clinical or subclinical neuropathy. Neuropathies are among the most common chronic complications of diabetes, affecting up to 50% of patients.[5]

Diabetes is the major cause for the development of Neuropathic pain. There are mainly 3 mechanisms for the development of neuropathic pain because of diabetes including microvascular damage, metabolic disorders and changes in the interactions between neuronal

Corresponding author: Dr. Mayuresh Dilip Kiran

and immunological systems in parallel with glial cell activation. First we are discussing the mechanism of microvascular damage for the development of diabetic neuropathy. In microvascular damage there is change in the blood vessels supplying the peripheral nerves. These changes are based on increase in the wall thickness with the hyalinization of the vessel wall and basal lamina of the arterioles and capillaries which leads to nerve ischemia. Through revised primary capillary membrane to the endoneurium penetrates the plasma protein, causing swelling and increased interstitial pressure in the nerves and capillary pressure, fibrin deposition as well as thrombus formation. Proximal and distal segments of the nerve shows multifocal fibre loss along the length of the nerves which leads to the diabetic neuropathic pain. The second mechanism for the diabetic neuropathy is metabolic disorders. Hyperglycemic state in the type 1 diabetes which is responsible for the enhanced activation of polylol pathway (Fig. 1). In the hyperglycemic state, the affinity of aldose reductase for glucose is increased which leads to the increased production of sorbitol. Sorbitol doesn't cross cell membranes and gets intracellularly accumulated in the nervous tissue, thus generates osmotic stress. Osmotic stress increases the intracellular water influx and fluid molarity, nerve fibre degeneration and Schwann cell damage. Furthermore, upregulation of the NADPH oxidase complex results in oxidative stress through reduced glutathione production, decreased nitric oxide concentrations and increased reactive oxygen species concentrations (Fig. 1). Free radicals, oxidants, and some unidentified metabolic factors activate the nuclear enzyme poly (ADP-ribose) polymerase (PARP), which is a fundamental mechanism in the development of diabetic neuropathy.[6]

In third mechanism, non-neuronal cells (microglia, astrocytes and immune cells) are activated under the hyperglycemic condition in the spinal cord, plays an important role in the spinal cord. Active glial cells, particularly microglia, which are resident macrophages of the central nervous system, are responsible for signalling between components of the nervous and immune systems. Microglia is responsible for the initiation of neuropathic pain.[6]

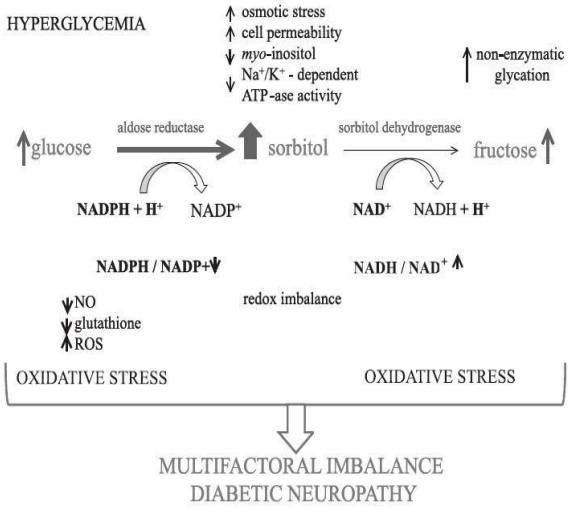

Figure 1: Multifactorial etiology of diabetic neuropathy. Hyperglycemia leads to enhanced activation of the polyol pathway, oxidative stress and non-enzymatic glycation. These factors either interact or independently function toward the development of diabetic neuropathy, directly affecting nerve tissues or nutrient vascular tissues [6]

The management of neuropathic pain goals in patients include blood glucose control and symptomatic pain relief. With regard to pain modulation, 50% reduction in pain, regardless of the baseline pain score, is considered a "meaningful" reduction in patients with neuropathic pain.[5]

National Institute for Health and Care Excellence (NICE) [7] and Canadian Pain Society (CPS) [8] have recommended amitriptyline, a tricyclic antidepressant (TCA), as the first line drug for the neuropathic pain due to DPN; however titration to higher doses is limited by its anticholinergic adverse effects. Studies have demonstrated that the TCAs provide moderate to good relief of pain in patients with painful DPN. These drugs relieve pain independent of their antidepressant effects.[9]

The management of patients with neuropathic pain is challenging. As per the 18th edition of

Harrison's Textbook of Internal Medicine, amitriptyline is of a particular value in the management of neuropathic pain for which there are few other therapeutic options. Pregabalin is an Anticonvulsant which is used in treatment of neuropathic pain as well. National Institute of Clinical Excellence (NICE) and Canadian Pain Society (CPS) recommends amitriptyline and pregabalin as first-line treatment of neuropathic pain. Further the NICE and CPS guidelines also recommend the use of combination of amitriptyline and pregabalin in patients with pain not controlled on monotherapy of the individual drugs.[10]

There are mainly 3 mechanism of actions of Tricyclic antidepressents which are useful in the treatment of neuropathic pain including 1)Sodium channel blockade is similar to the local anaesthetics, 2)Blockade of Serotonin receptors – 5-HT2A, 5-HT2C, 5-HT3, 5-HT6 and 5-HT7 and 3)Inhibition of Nicotinic Acetylcholine Receptors. [8]

Pregabalin is a structural derivative of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). The predominant mechanism of action is thought to be through its presynaptic binding to the α2δ subunit of voltage- gated calcium channels which in turns leads to reduced release of neurotransmitters, eg, glutamate, substance P, and calcitonin gene-related peptide. Pregabalin does not appear to act through the GABAergic neurotransmitter system and it has been shown to act on voltage-gated potassium channels.[11]

For the management of the neuropathic pain in patients with pain not controlled on monotherapy of the individual drug, Centaur pharmaceuticals has developed AmNurite P which is a combination of amitriptyline 10mg and pregabalin 75mg SR.

Pregabalin is having a short plasma half-life of 5–6.5 hours where as amitriptyline is having the plasma half life of 21 hours (range 13-36 hours).[12,13] So that while formulating the fixed dose combination pregabalin was formulated as a sustained release tablet which will release the drug slowly and amitriptyline was formulated as a conventional tablet which will release the drug of more than 75% in less than 45 min.

Materials and Methods

To evaluate the efficacy and safety, a three week study was conducted on 1269 patients on adults of either sex or age with Neuropathic pain in 120 trial centers. Patients satisfying the inclusion and exclusion criteria were been enrolled in the study. Inclusion criteria were that a volunteer should be over 18 years of age; should have neuropathic pain due to Diabetic peripheral Neuropathy, Low Back Pain, Post Herpatic Neuralgia, Fibromyalgia and Spinal Cord Injury. If the patient is Diabetic, specific treatment for Diabetes with Antidiabetics is being taken, If on other drugs neuropathic pain was not controlled by single neuroanalgesic and the patients who willing to adhere to the protocol of the study. Subjects were excluded if patients is having hepatic or renal impairment, pregnant or breast Feeding women, any evidence of Psychological disorder, Patients taking MAO inhibiting drugs or patients having history of urinary retention. For the study Drs having speciality neurology, diabetology and internal medicine were selected. The entries were recorded in the case record form by the investigator. The accuracy of all data on the CRF was attested by the signature of the investigator.

Patients were screened during Visit 1 at baseline and who fitted with the inclusion and exclusion criteria were enrolled in the study. Patients were treated with the study medication of AmNurite P (combination of amitriptyline and pregabalin). The efficacy and safety was assessed on two visits at Visit 2 (day 7) and Visit 3 (day 21). Pain was assessed by a 10 point Numerical Pain Intensity Scale or the visual analogue scale (VAS), the patients were asked to rate their pain and the corresponding visual analogue score was recorded by the investigator. The pain assessed during the first visit before treating any medication was served as the baseline score. The nature and severity of the adverse events reported were assessed at the end of the study.

The primary outcome measure was the change in the pain level by the VAS score at Visit 2 on day 7 and Visit 3 on day 21 as compared to the baseline on visit 1. Secondary outcome measures included reporting of the adverse events that were either spontaneously reported by the patient or noticed by the physician during the trial and safety was recorded. All the data were evaluated statistically.

Statistical analysis was done by various ways including change in mean VAS score from baseline to visit 2 to visit 3, percentage of patients who had ≥50% reduction in neuropathic pain as compared to the baseline at visit 2 and visit 3, risk reduction and number needed to treat were calculated for the patients who had more than 50% decrease in the neuropathic pain at visit 3. Further 3 statistical evaluations were done to evaluate whether the decrease in the neuropathic pain depends on blood glucose control (normoglycemic diabetic patients / hyperglycemic diabetic patients), age (age below or above 60) or gender (male / female).

For evaluating the effect of blood glucose control on pain relief, fasting and post-prandial blood glucose (FPG and PPG) were measured on baseline and at the end of the study (visit 3). Based on blood glucose level two groups were done named as group 1, a group of normoglycemic patients and group 2, a group of hyperglycemic patients in which the limit for normoglycemic patients were kept as fasting blood glucose level ≥100 mg/dl and postprandial plasma glucose ≥140 mg/dl. And then the change in the mean VAS score at visit 2 and visit 3 as compared to the baseline were evaluated in both the groups.

For evaluating the effect of age on neuropathic pain relief, patients data were divided into the two groups as the patients of age below 60 and above 60. And then the change in the mean VAS score at visit 2 and visit 3 as compared to the baseline were evaluated.

The same procedure was followed for evaluating the effect of gender on neuropathic pain relief, patients data were divided into the two groups of male and female patients and then the change in the mean VAS score at visit 2 and visit 3 as compared to the baseline were evaluated.

Result:

Change in mean VAS score from baseline to visit 2 to visit 3 is depicted in figure 2.

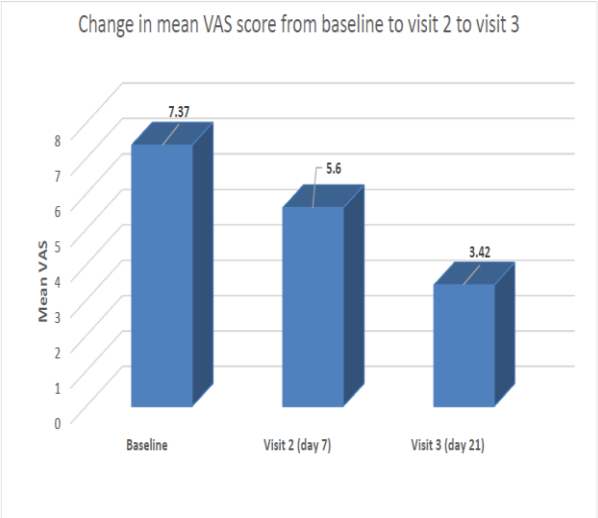

Figure 2: Change in mean VAS score from baseline to visit 2 to visit 3

Percentage of patients who had ≥ 50% reduction in neuropathic pain in visit 2 and visit 3 as compared to baseline is depicted in the figure 3

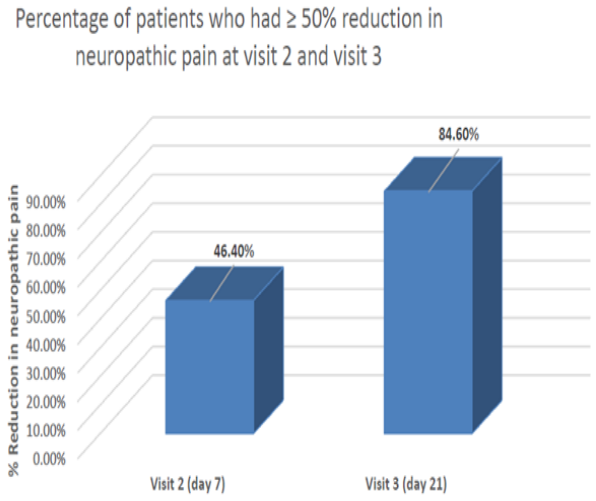

Figure 3: Percentage of patients who had ≥ 50% reduction in neuropathic pain at visit 2 and visit 3

Risk reduction and number needed to treat for the patients who had more than 50% reduction in neuropathic pain at visit 3 is mentioned in the following table no. 1

Table no.1 Risk reduction and number needed to treat for the patients who had more than 50% reduction in neuropathic pain at visit 3

% of patients who had more	RR	NNT
84.60 %	0.846	1.19

Comparison of reduction in mean VAS score from baseline to visit 2 to visit 3 in normoglycemic and hyperglycemic patients is depicted in figure 4.

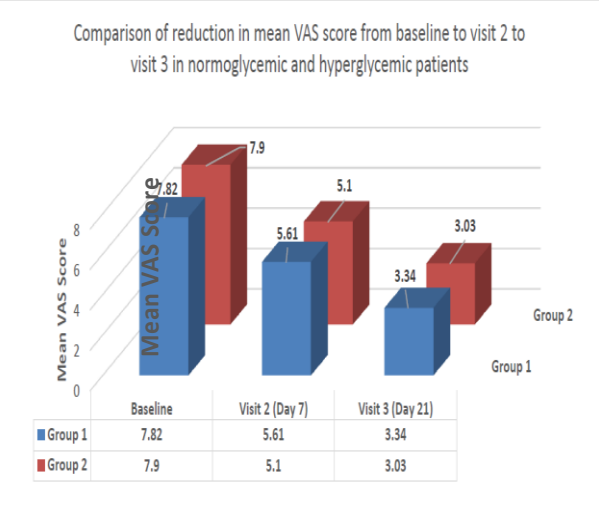

Figure 4: Comparison of reduction in mean VAS score from baseline to visit 2 to visit 3 in normoglycemic and hyperglycemic diabetic patients

Comparison of reduction in mean VAS score from baseline to visit 2 to visit 3 in patients of age below and above 60 is depicted in figure 5.

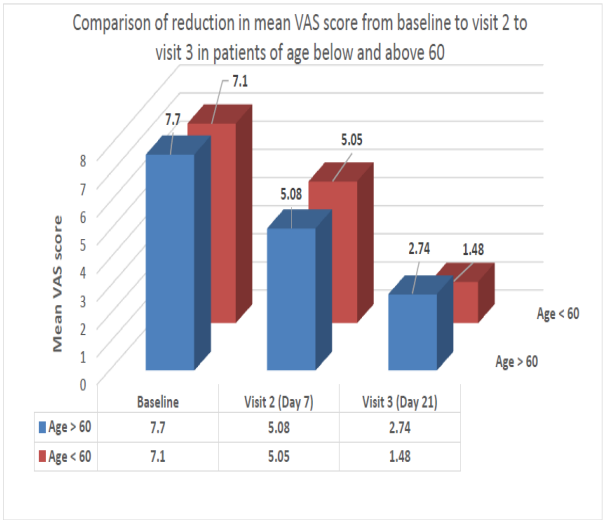

Figure 5: Comparison of reduction in mean VAS score from baseline to visit 2 to visit 3 in patients of age below and above 60

Comparison of reduction in mean VAS score from baseline to visit 2 to visit 3 in male and female patients is depicted in the figure no. 6

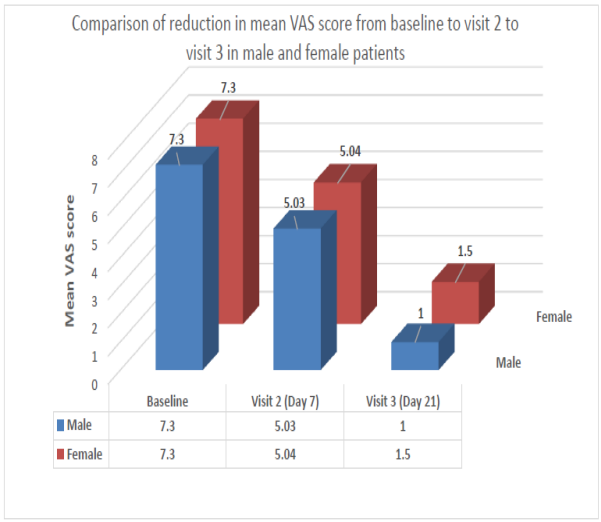

Figure 6: Comparison of reduction in mean VAS score from baseline to visit 2 to visit 3 in male and female patients

Discussion

As per the literature the combination of amitriptyline and pregabalin is effective and efficacious in the treatment of neuropathic pain which is not controlled by the carbamazepine 14

In the first statistical evaluation we have analysed that mean VAS score at baseline was 7.87 which was decreased to 5.6 at visit 2 on day 7 which was further decreased to 3.4 at visit 3 on day 21. It clearly states that AmNurite P a combination of amitriptyline and pregabalin is effective in reducing the neuropathic pain intensity which proves its efficacy in reducing the pain.

In the second statistical evaluation we have calculated the percentage of patients who had more than 50% decrease in the neuropathic pain as compared to the baseline in visit 2 and visit 3. As per the results in visit 2 and visit 3 we found 46.40% patients and 84.60% patients respectively. Which states that the AmNurite P was having good efficacy in reducing neuropathic pain intensity of more than 50%.

In 4^{th}, 5^{th} and 6^{th} statistical evaluation we have divided the patients data into two groups for each evaluation by taking blood glucose level,

age and gender as a differentiating factor respectively. And we found that the AmNurite P was effective in reducing the pain in diabetic patients who had maintained the normal glucose and also the hyperglycemic patients. Mean change in VAS score in group 1 and group 2 were comapratively similar at visit 2 and visit 3. These results suggested that the analgesic effects of this combination is independent of blood glucose control. Similarly not much difference was found in pain relief when the patients data were based on age. AmNurite P therapy was demonstrated similar type of pain reduction in patients of age more than or less than 60 years. However at visit 3 VAS score was comparatively less in patients of age <60 years compared to age >60 years (1.48 vs 2.74). So it clarifies that the therapy of AmNurite P is independent of age in reducing pain. AmNurite P was also effective in reducing the neuropathic pain irrespective of gender as both male and female patients showed reduction in neuropathic pain.

Conclusion:

The AmNurite (combination of amitriptyline 10/25 mg and mecobalamin 1500 mcg) was found to be safe and efficacious in the management of neuropathic pain.

References

1. John Scadding. Neuropathic Pain. ACNR. 2003;3:8-14
2. Neuropathic Pain Management http://www.webmd.com/pain-management/guide/neuropathic-pain
3. DE Moulin, AJ Clark, I Gilron, MA Ware, CPN Watson, BJ Sessle, T Coderre, PK Morley-Forste, J Stinson RN, A Boulanger, P Peng, GA Finley. Pharmacological management of chronic neuropathic pain – Consensus statement and guidelines from the Canadian Pain Society. Pain Research and Management. 2007;12:13-21
4. The current state of diabetes mellitus in India. Australasian Medical Journal. 2014;7:45–48.
5. Jorge R Miranda-Massari, Michael J Gonzalez, Francisco J Jimenez, Myriam Z Allende-Vigo, Jorge Duconge. Metabolic Correction in the Management of Diabetic Peripheral Neuropathy: Improving Clinical Results Beyond Symptom Control. Curr Clin Pharmacol. 2011;6:260–273
6. Magdalena Zychowska, Ewelina Rojewska, Barbara Przewlocka, Joanna Mika. Mechanisms and pharmacology of diabetic neuropathy – experimental and clinical studies 2013;65:1601-1610
7. Neuropathic pain – pharmacological management. NICE clinical guideline 173. Issued: November 2013 last modified: December 2014
8. DE Moulin, AJ Clark, I Gilron, MA Ware, CPN Watson, BJ Sessle, T Coderre, PK Morley-Forste, J Stinson RN, A Boulanger, P Peng, GA Finley. Pharmacological management of chronic neuropathic pain – Consensus statement and guidelines from the Canadian Pain Society. Pain Res Manage. 2007;12:13-21
9. Robert J. Tanenberg. Diabetic Peripheral Neuropathy: Painful or Painless. Hospital Physician 2009:1-8
10. T. R. Harrison. Harrison's Principles of internal medicine. 18th edition. Mc Graw Hill.
11. Nanna B Finnerup, Troels S Jensen. Clinical use of pregabalin in the management of central neuropathic pain. Neuropsychiatric Disease and Treatment 2007:3(6) 885–891
12. Yasmin U Dongre, Onkar C Swami. Sustained-release pregabalin with methylcobalamin in neuropathic pain: an Indian real-life experience. International Journal of General Medicine 2013:6 413–417
13. Amitriptyline hydrochloride.www.inchem.org /documents/ukpids/ukpids/ukpid18.htm
14. Ahmed O Lawal, Akinyele O Adisa, Akindayo O Akinyamoju, Bamidele Kolude. Management of Trigeminal Neuralgia using Amitriptyline and Pregablin combination Therapy. Afr. J. Biomed. Res. 2012;15: 201-203