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# INFLAMMATORY BIOMARKER ASSOCIATED VARIABILITY IN THE PHARMACODYNAMIC RESPONSE TO GABAPENTIN IN DIABETIC PERIPHERAL NEUROPATHY

**Dr. Thatikonda Keerthi*[1], Dr. G Suhasin[2]**

[1*]Research Scholar, Department of Pharmacology, GITAM School of Pharmacy, GITAM University- Visakhapatnam, Andhra Pradesh 530045, India, Email : kthatiko@gitam.in
[2]Associate Professor, Department of Pharmacology, GITAM School of Pharmacy, GITAM University- Visakhapatnam, Andhra Pradesh 530045, India.

## ABSTRACT

**Background:** Chronic neuropathic pain is largely caused by diabetic peripheral neuropathy (DPN), a frequent microvascular condition associated with diabetes mellitus. Gabapentin is widely used for the management of painful DPN; however, its pharmacodynamic response may vary depending on the severity of neuropathy and clinical status of the patient. To evaluate the pharmacodynamic profile of gabapentin with reference to diabetic peripheral neuropathy status.

**Methods:** A prospective, observational, comparative analytical investigation was carried out involving 76 patients, with 19 individuals in each of the four study groups: non-diabetic individuals with neuropathy, diabetic patients experiencing non-diabetic neuropathies, diabetic patients suffering from diabetic peripheral neuropathy, and diabetic peripheral neuropathy patients undergoing emergency surgical procedures. The pharmacodynamic evaluation included assessing pain intensity using the Visual Analogue Scale (VAS), along with glycaemic parameters and inflammatory biomarkers. The results were analyzed and compared across the four different study groups.

**Results:** Patients suffering from diabetic peripheral neuropathy showed notably elevated pain levels, less effective glycaemic control, and altered levels of inflammatory biomarkers when compared to the other groups ($P < 0.05$).The greatest pharmacodynamic changes were observed in patients with diabetic peripheral neuropathy undergoing emergency surgery. These findings indicate that the clinical response to gabapentin varies according to DPN status.

**Conclusion:** The pharmacodynamic profile of gabapentin differs with extentof DPN. Individualized treatment based on neuropathy status may improve pain control and optimize therapeutic outcomes.

**KEYWORDS:** Diabetes mellitus; Diabetic peripheral neuropathy; Gabapentin; Inflammatory biomarkers; Neuropathic pain; Pharmacodynamics; Visual Analogue Scale

## INTRODUCTION

Gabapentin is the first choice for treatment of painful diabetic peripheral neuropathy primarily because ofits safety and efficacy.1,2,3 Gabapentin mainly binds to the α2δ-1 subunit of presynaptic voltage-gated calcium channels in the central nervous system to produce its pharmacological effects. This interaction reduces the amount of calcium that enters presynaptic neurons, which in turn reduces the release of excitatory neurotransmitters such substance P, glutamate, and calcitonin gene-related peptide (CGRP). Overall result is a decrease in neuronal hyperactivity, lessened central sensitization, and relief from neuropathic pain.4,5

Given its structural similarity to γ-aminobutyric acid (GABA), one might expect gabapentin to bind to GABA receptors or be metabolized to GABA. However, gabapentin neither binds directly to GABA receptors nor is it converted to GABA. In contrast, it indirectly enhances inhibitory neurotransmission and alters the neural pathways associated with pain processing in both the spinal cord and the brain.

Disease-related factors play a role in altering the pharmacodynamic reaction to gabapentin. For example, in diabetic peripheral neuropathy, persistent hyperglycaemia results in oxidative stress, neuroinflammation, microvascular dysfunction, mitochondrial damage, and ongoing axonal degeneration. As a consequence, neuronal excitability is altered and there is increased expression of the α2δ-1 calcium channel subunit. Such pathological events may change the way injured nerves react to gabapentin and lead to substantial variability among patients in terms of analgesic efficacy.6,7,8

Moreover, other disease characteristics such as the length of time a person has had diabetes, the extent of neuropathy, the level of glycaemic control, inflammatory condition, and the presence of other diseases may also change the amount of pain relief a person experiences from treatment with gabapentin.

Pharmacodynamic study of gabapentin involves more than just determining drug levels in plasma, but also evaluates clinical and biological effects. Factors like pain severity using theVisual Analogue Scale (VAS), daily activity and sleep effectiveness, and changes in TNF-α, interleukin-6 (IL-6), and C-reactive protein (CRP). Provide measurable indicators of treatment effect.Connecting these pharmacodynamic results with pharmacokinetic data could lead to the understanding of gabapentin's exposure-response relationship and the variation in treatment outcomes of diabetic peripheral neuropathy patients.2,3

Although gabapentin is commonly used to treat neuropathic pain in diabetes, scant research directly explores how the severity of neuropathy affects the drug's pharmacodynamics and the possible connection to pharmacokinetic variability. Hence, examining differences in pharmacokinetic and pharmacodynamic features of gabapentin with regard to diabetic peripheral neuropathy may pave the way for personalized dosing, better pain management, fewer side effects, and overall optimized results in diabetic patients.

## MATERIALS AND METHODS

This prospective, observational, comparative analytical study was carried out at a tertiary care hospital over the course of 32 months, from March 2022 to October 2024 at Kamineni Hospitals, Hyderabad. The study was approved ethically from the same hospital (ECNEWIINST/202/1/1676). Eligible participants were 18 to 65 years old, of either gender, newly started on gabapentin, and had normal liver and kidney function. Patients were divided into four groups: Group 1 comprised patients with neuropathy who were not diabetics; Group 2 comprised diabetics with non-diabetic neuropathies; Group 3 comprised diabetics with diabetic peripheral neuropathy (DPN); and Group 4 comprised patients with DPN who were undergoing emergency surgery.Exclusion criteria were prior gabapentin use, severe hepatic or renal impairment, pregnancy or lactation, gabapentin hypersensitivity, significant comorbidities other than diabetes, pre-existing opioid therapy, elective surgery, or refusal to provide informed consent. Demographic details, medical history, physical examination results, and baseline laboratory results (complete blood count, liver and renal function tests, HbA1c, blood glucose, and blood pressure) were collected after written informed consent was obtained. All participants received gabapentin 200 mg orally once daily. Pharmacodynamic evaluation included pain assessment using the Visual Analogue Scale (VAS), blood glucose measurement, and analysis of pain and inflammatory biomarkers (CRP, TNF-α, IL-6). Based on previous data, the minimum sample size was 19 participants per group. IBM SPSS Statistics version 24.0 was used for the statistical analysis. The Chi-square or Fisher's exact test were used to compare the qualitative variables, which were expressed as frequency and percentage. Quantitative variables were expressed as mean ± standard deviation and examined using one-way ANOVA, paired t-test, or independent t-test, along with non-parametric testing when necessary. Statistical significance was defined as a P value of $<0.05$.

## RESULTS

Group 1 (non-diabetic patients with neuropathy), Group 2 (diabetic patients with non-diabetic neuropathies), Group 3 (diabetic patients with diabetic peripheral neuropathy), and Group 4 (diabetic peripheral neuropathy patients undergoing emergency surgery) comprised the four groups of 19 patients each in the current study.The study evaluated the pharmacodynamic profile of gabapentin among these four groups using demographic, clinical, biochemical, and pharmacodynamic parameters.

The study mean age varied between 47.95 and 51.21 years, and there was no significant difference across the groups ($P = 0.722$). Similarly, the height difference was not statistically significant ($P = 0.105$).There were statistically significant differences in body weight and body mass index (BMI) across the groups ($P = 0.001$).Group 2 had the highest average body weight and BMI, whereas Group 3 had the lowest mean body weight.overall, demographic characteristics were similar except foranthropometric measurements. The same was summarised in Table 1.

Significant statistical differences were found for HbA1c, random blood glucose (GRBS), and duration of diabetes between the study groups ($P < 0.001$). Group 4 mean was the highestin HbA1c, GRBS, and diabetes duration, followed by Groups 3 and 2, whereas Group 1 had normal glycemic parameters and no diabetes history. The study population had fair renal function, as seen by the estimated glomerular filtration rate (eGFR), which did not differ substantially across groups ($P = 0.117$).Data for Baseline Clinical and Biochemical Characteristics were summarised in Table 2.

Mean Visual Analogue Scale (VAS) scores increased steadily from Group 1 to Group 4, the highest pain intensity being found in diabetic peripheral neuropathy patients undergoing emergency surgery ($P < 0.001$). Inflammatory biomarkers like TNF-α, IL, and CRP showed significant variations ($P < 0.001$).Data presented in Table 3.

## DISCUSSION

Diabetic peripheral neuropathy (DPN) is the most common long-term microvascular consequence of diabetes mellitus, a chronic metabolic disease. Development and progression of DPN are influenced by several factors such as poor glycaemic control, duration of diabetes, metabolic abnormalities, and inflammatory processes. As patient characteristics and disease severity can affect both the pharmacokinetic and pharmacodynamic profiles of gabapentin, it is therefore necessary to compare baseline demographic, clinical, and pharmacodynamic parameters among the study groups in order to interpret a treatment response and consider the variability of drug effects1,2,6.

The four study groups in the current investigation had comparable patient mean ages. No statistically significant difference was observed, indicating that age was not a factor in contributing to the pharmacodynamic changes seen. The baseline demographic characteristics of patients with painful diabetic peripheral neuropathy receiving gabapentin therapy were found to be similar was reported by Backonja et al1.,andGómez-Pérez et al2. Height across the study groups was also similar. However, body weight and BMI differed significantly. Group 2 had the greatest average weight and BMI, whereas Group 3 had the lowest average weight.

Th our study demonstrated significant difference in baseline clinical and biochemical characteristics among study groups. HbA1c, GRBS, and diabetes duration showed a steady increase from Group 2 to Group 4, the highest values observed diabetes peripheral neuropathy patient undergoing emergency surgery. Similar findings were reported by Pop-Busi et al.,6and Tesfaye et al.,7 who showed that long-term diabetes and chronic hyperglycemia are significant risk factors for the development and progression of diabetic peripheral neuropathy. In contrast, estimated glomerular filteration rate

(eGFR) remained comparable among the study groups, suggesting preserved renal function. Since gabapentin is eliminated unchanged through renal excretion, comparable renal function across the groups minimizes the influence of renal clearance on pharmacokinetic variability and strengthens the validity of comparisons between the study groups, as also described by Hemstreet3.

Assessment of pharmacodynamic parameters revealed significant differences in pain severity inflammatory markers among the four study groups. The Visual Analogue Scale (VAS) scores increased progressively from Group 1 to Group 4, indicating greater pain intensity with increasing severity of diabetic peripheral neuropathy. These findings are comparable with those of Backonja et al1., who found that individuals with painful diabetic neuropathy had higher baseline pain levels and saw considerable improvement after gabapentin treatment.Inflammatory markers like C-reactive protein (CRP), interleukin (IL), and tumor necrosis factor alpha showed Significant differences.Chronic hyperglycemia is known to promote oxidative stress and activation of inflammatory pathways, resulting in increased production of pro-inflammatory cytokines that contribute to peripheral nerve damage and neuropathic pain. Similar findings have been described by Feldman et al8., and Pop-Busui et al6., who emphasized the role of inflammation in the etiology of diabetic neuropathy. The observed differences in pain intensity and inflammatory markers among the study groups suggest that the pharmacodynamic response to gabapentin may vary according to the severity and clinical status of diabetic peripheral neuropathy. These findings support the concept that individualized treatment stratergies based on patient characteristics and disease severity may optimize the therapeutic effectiveness of gabapentin in patients with diabetic peripheral neuropathy.7,8

## CONCLUSION

Variations in clinical and pharmacodynamic parameters among patients of different diabetic peripheral neuropathy status were identified by this presentstudy. Inadequate glycaemic control, longer duration of diabetes, and increased pain intensity severity were associated with more advanced neuropathy. These observations suggest that diabetic peripheral neuropathy status may influence pharmacodynamic features of gabapentin, hence the understanding and implementation of individualized treatment is necessary in order to optimize pain management and improved clinical results.

**Conflict of interest**
Authors declare no conflict of interest

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Nil

## ABBREVIATIONS

| Abbreviation | Full form |
|---|---|
| ANOVA | Analysis of Variance |
| BMI | Body Mass Index |
| CBC | Complete Blood Count |
| CGRP | Calcitonin Gene-Related Peptide |
| CNS | Central Nervous System |
| CRP | C-Reactive Protein |
| DPN | Diabetic Peripheral Neuropathy |
| eGFR | Estimated Glomerular Filtration Rate |
| GABA | Gamma-Aminobutyric Acid |
| GRBS | Random Blood Sugar |
| HbA1c | Glycated Hemoglobin |
| IBM | International Business Machines |
| IL | Interleukin |
| IL-6 | Interleukin-6 |
| SD | Standard Deviation |
| SPSS | Statistical Package for the Social Sciences |
| TNF-α | Tumor Necrosis Factor-Alpha |
| VAS | Visual Analogue Scale |

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## AUTHOR CONTRIBUTIONS

Dr. Keerthi Thatikonda: Conceptualization, methodology, data collection, investigation, formal analysis, and writing, original draft preparation.
Dr. G. Suhasin: Supervision, methodology, project administration, validation, review and editing of the manuscript, and overall guidance and monitoring of the study.
All authors have read and approved the final version of the manuscript.

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