Research Article

Evaluation of pharmacokinetic parameters for gabapentin in diabetic neuropathy patients with two different drug regimens

T. Rujaswini[1], D. Praveen[2], P. Ranadheer Chowdary[2], M. Vijey Aanandhi[3]*

ABSTRACT

Aim and Objectives: The main aim of the study is to evaluate the pharmacokinetic parameters for gabapentin in diabetic neuropathy (DN) patients with two different drug regimens. The objective of the present study was to evaluate the potentiality of the gabapentin in DN affected people. **Methodology:** The sample size chosen was 10 patients. The study design followed was open-labeled, randomized controlled, pilot study. Patients were separated based on the oral glycemic agent administration. Group A includes 5 patients using metformin, sitagliptin, and gabapentin, whereas Group B with 5 patients using metformin, glibenclamide, and gabapentin. Blood samples were collected with the time interval of 0 h, 30 min, 1, 2, 3, 6, 12, and finally at the 24th h after the dosing to evaluate pharmacokinetic parameters of the single-dose administration. Area under the concentration-time curve (AUC) from time 0 to 24 h (AUC_{0-t}), AUC from zero to infinity ($AUC_{0-\infty}$), the peak plasma concentration of the drug (C_{max}), and the time needed to achieve C_{max} (T_{max}) are assayed to determine the efficacy of the treatment with gabapentin. Liquid chromatography-mass spectrometry is the technique used in evaluating the pharmacokinetic parameters of dose concentration of gabapentin in DN patients along with two different dosage regimens. **Results:** Of 10 patients selected, 6 male patients and 4 female with diabetic were participated in the study. Baseline parameters such as age, duration of diabetes mellitus, duration of metformin use, C-reactive protein, and homocysteine level were checked for the patients. The total area for Group A was found to be 174.06, whereas in Group B was 125.32 for this *P*-value found to be 0.001, which is more statistically significant. C_{max} of Group A was 19.1 and Group B was 13.1 which are within the therapeutic range of 2–20 µg/ml. AUC, T_{max}, and C_{max} were within the acceptable range. **Conclusion:** In our study, Group A (sitagliptin) shows an increase in AUC value and also increase in C_{max} and T_{max}. Hence, this may enhance increased therapeutic efficacy of the drug, and no serious adverse events were reported. Hence, this regimen may be pharmacokinetically superior to the regimen containing glibenclamide (Group B).

KEY WORDS: Diabetic neuropathy, Gabapentin, Liquid chromatography-mass spectroscopy, Oral hypoglycemic agents, Pharmacokinetic parameters

INTRODUCTION

Uncontrolled diabetes leading to nerve dysfunction and this condition is known as diabetic neuropathy (DN).[1] Roughly 50% of patients with diabetes suffer from DN. DN is associated with peripheral nerve dysfunction and is the greatest source of morbidity and mortality in diabetic individuals.[2] Nerve fibers carry pain signals that run throughout the body. The nerve fibers are very sensitive to high glucose levels. Due to high glucose levels, nerve dysfunction occurs slowly. The risk of diabetic nerve pain is higher if the patient with poor blood glucose control, diabetic for a long time, and smoker.

Nerves to the feet are longer in the body. Due to high blood glucose levels ends of the longest nerve fibers get damaged first, that is, the reason pain is often felt first in the feet. Numbness, tingling, burning, pricking, cramping, lack of muscle control, and extremely sensitive to touch are few symptoms of pain due to nerve damage. Diabetic neuropathic pain is often worse at night; as a result, sleep disturbances occur.

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[1]Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai, Tamil Nadu, India, [2]Research Scholar, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai, Tamil Nadu, India, [3]Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai, Tamil Nadu, India

***Corresponding author:** Dr. M. Vijey Aanandhi, Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Chennai, Tamil Nadu, India. E-mail: hodpchemistry@velsuniv.ac.in

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If pain is long-lasting, pain-relieving agents are not solely the goal of treatment. The foremost measure to be taken in DN patients is a blood sugar level control to prevent further nerve damage.[3] Exercise, high fiber, and healthy diet should be included in daily routine life to keep blood glucose levels normal. The American Diabetic Association recommends at least ½ h of exercise per day for diabetes. If numbness at foot present, then percutaneous electrical nerve stimulation was to be considered as a part of treatment for DN.[4]

Oral Hypoglycemic Agents

Approximately 200 million people suffer from type 2 diabetic mellitus worldwide.[5] To avoid microvascular and macrovascular complications, goal is to maintain blood glucose level control by diet and exercise along with oral hypoglycemic agents. Hypoglycemic agents are classified into 7 distinct classes that include biguanides, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, incretin mimetics, and dipeptidyl peptidase 4 (DPP-4) inhibitors.[6] Few effective oral hypoglycemic agents used for the study are metformin, sitagliptin, and glibenclamide.

Metformin belongs to biguanide class of medications. It is one of the usual medicines used in the treatment of type 2 diabetes. It primarily decreases hepatic glucose production by adenosine monophosphate-activated protein kinase. It decreases intestinal absorption of glucose and thereby increases insulin-mediated glucose uptake.[7] It is metabolized by the CYP450 pathway and this is excreted unchanged in the urine. Metformin half-life is roughly 6.2 h.[8] Chances of increase in the risk of sensory, autonomic, and motor neuropathy in diabetes using metformin for more than 6 months were reported due to increase in the level of homocysteine, thereby reduced levels of vitamin B_{12} both contributing factors to neuropathy.[9] Studies show that folate supplement helpful in reducing this neuropathic pain.

Sitagliptin belongs to the class of DPP-4 inhibitors or gliptins. It increases incretin levels that are glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. They inhibit glucagon release, which can cause an increase in insulin secretion, thereby decreasing the blood glucose levels in the body.[10] The dose of sitagliptin phosphate is 50–100 mg once daily. It can be taken with or without food. The bioavailability of siatagliptin is 87%; of this, it is confirmed that sitagliptin rapidly absorbed by oral administration.[11] The principal enzyme responsible for the metabolism of sitagliptin was CYP3A4, and roughly half-life is 12.4 h. About 79% of sitagliptin is excreted unchanged in the urine. Few experimental results indicate that the DPP-4 inhibitors improve not only the glycemic control but also blood pressure, lipid profiles, and quality of life.[12] A few studies show that patients taking metformin/sitagliptin together can inhibit the complication of diabetes, such as neural damage to some extent.[13]

Glibenclamide, also known as glyburide, belongs to the second-generation sulfonylureas. They function by stimulating insulin release from the insulin-secreting β-cells[14] by blocking ATP-sensitive potassium channels on the pancreatic cell surface. Sulfonylureas suppress hepatic glucose production. Sulfonylureas increase both basal and bolus insulin secretion. The onset of action takes place in 1 h, and peak plasma levels are reached within 2–4 h.[15] As glibenclamide shows longer half-life, it can be taken once daily. It is completely metabolized in the liver and excreted in urine and feces. A new look toward old therapy glibenclamide showing desirable decrease in fasting blood sugar, post-prandial blood sugar, and hemoglobin A1c levels.[16]

Treatment of DN

Diabetic neuropathic pain can be diagnosed by conducting a physical examination that is carefully assessing the symptoms and medical history. Overall muscle strength, tendon reflexes, sensitivity to touch, and vibration are few symptoms noted due to nerve

Table 1: Baseline parameters

Baseline parameters	Group A	Group B
Age	31.6±10.2	32.6±10.2
Male (6)	3	3
Duration of DM	4.1±0.6	3.7±0.2
Duration of metformin use	2.7±1.8	2.9±2.1
CRP	7.6±1.2	6.4±1.5
Homocysteine	14.2±2.7	13.6±1.7

All values are mean±SEM. DM: Diabetic mellitus, CRP: C-reactive protein

Table 2: Serum concentration of gabapentin

Time (hour)	Group A (µg/ml)	Group B (µg/ml)
0	0.0	0.0
½	0.7±0.1	0.4±0.1
1	1.9±0.3	0.9±0.2
2	3.1±0.6	2.7±0.5
3	7.1±0.4	5.4±0.2*
6	19.1±0.4	13.1±0.3*
12	6.3±0.3	4.7±0.2
24	2.1±0.2	1.7±0.3

All values are mean±SEM. *P<0.001 was considered to be statistically significant

Table 3: Pharmacokinetic parameters

Pharmacokinetic parameters	Group A	Group B	*P*
AUC_{0-t}	174.06±2.5	125.32±2.5	0.0001*
$AUC_{0-\infty}$	174.06±2.5	125.32±2.5	0.0001*
T_{max}	6±1.0	6±1.0	-
C_{max}	19.1±0.7	13.1±0.7	0.0001*

All values are mean±SEM. *P<0.001 was considered to be statistically significant. AUC: Area under the concentration-time curve

dysfunction. Sores on feet, skin cracks, blisters, bone, and joint problems also lead to DN.[17] The American Diabetes Association urges that all people with diabetes should have a related complete foot examination at least once in a year. Filament testing, quantitative sensory testing, nerve conduction studies, and electromyography are done to help diagnose DN.[18] No remedy was yet discovered for complete cure of DN pain. The goal of any treatment is to control blood sugar level, relieve pain, and manage further complications. The recommended target blood sugar levels before meals are between 80 and 130 mg/dl and <180 mg/dl 2 h after meals.[19]

Self-care in diabetes management by improving blood sugar control can reduce the complications of neuropathic pain. Few nerve pain medications that can block the pain caused by damaged nerves are anticonvulsants, analgesics, anesthetics, and antidepressants.[20] Anticonvulsive agents not only relieve seizures but also used to treat nerve pain. Pregabalin, gabapentin, and carbamazepine are employed anticonvulsive drugs for the treatment of DN.[21] Serotonin-norepinephrine reuptake inhibitors were also employed for controlling neuropathic pain in diabetes.[22] Alternative medicines such as capsaicin cream on the skin, alpha-lipoic acid (antioxidant), transcutaneous electrical nerve stimulation, and acupuncture are few temporary pain-relieving agents.[23]

In my present study, I had worked on the effect of gabapentin in the DN. Gabapentin is a gamma-aminobutyric acid (GABA) analog, which works on the brain and nervous system. It is neither a GABA agonist nor antagonist. GABA is a neurotransmitter that acts as a "natural nerve-calming agent." Gabapentin increases the rate of synthesis of GABA in the brain, which probably increases the concentration of GABA.[2] Gabapentin is an anti-convulsive medication used in the treatment of partial seizures and also in neuropathic pain. Gabapentin interrupts the series of events that leading to neuropathic pain. It is one of the frequently prescribed drugs in the treatment of neuropathic pain caused by DN, post-therapeutic neuralgia, and central neuropathic pain.[24] It interacts with cortical neurons and inhibits auxiliary subunits of voltage-gated calcium channels. It stabilizes the electrical activity in the brain and affects the way that nerves sending messages to the brain. It binds to adenosine A1 receptor causing presynaptic inhibition of excitatory neurotransmitter release, i.e., glutamate, thereby reducing the neuropathic pain.[25] The minimum effective dose of gabapentin is 300 mg for neuropathic pain. Gabapentin is saturable and does not show any non-linear absorption kinetics where its bioavailability decreases as the dose increases. Gabapentin is eliminated unchanged in urine. The elimination half-life is roughly 5–7 h.[26] The clearance rate of gabapentin is 190 ml/min. Gabapentin is assayed in plasma using the high-performance liquid chromatography (HPLC) and LC-mass spectroscopy (LC/MS).[27] In the evaluation of drugs, pharmacokinetic parameters are considered for the best outcome.

Pharmacokinetic Parameters

The pharmacokinetics can be simply known as the way the body acts on the drug administered. It is concerned with the movement of the drug into, through, and out of the body. It is currently defined as the measure of the rate of absorption, distribution, metabolism, and excretion of drugs administered.[28] The application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient is known as clinical pharmacokinetics. All four processes involve drug movement across the membranes. Drug dissolves into the lipid bilayer to cross the membrane, and hence lipid-soluble drugs cross directly, whereas polar drugs do not. Few pharmacokinetic parameters analyzed in the present study of the drug administered are as follows: [29]

- Dosage of drug (D) - amount of drug administered
- Dosing interval (τ) - time between drug-dose administration
- C_{max} - the peak plasma concentration of the drug after administration
- T_{max} - time to reach peak plasma concentration of drug
- C_{min} - the trough concentration that the drug reaches before the next dose administered
- Area under the concentration-time curve (AUC) - the area under the plot of plasma concentration of a drug versus time after dose administration.

Aim

The main aim of the study is to evaluate the pharmacokinetic parameters for gabapentin in DN patients with two different drug regimens.

Objectives

The objectives of this study are as follows:

- To evaluate the potentiality of gabapentin in DN patients
- To investigate the pharmacokinetic parameters of gabapentin along with two different dosage regimens in DN patients.

METHODOLOGY

Study Site

The study was carried out in the General Medicine department of a tertiary care hospital.

Study Design

The study design involves an open-labeled, randomized controlled study.

Study Duration

The duration of the study was during September 2018–April 2019.

Sample Size

As it is a pilot study, the sample size chosen was 10 patients.

Groups	Number of patients	Treatment involved
Group A	5 patients	Metformin, sitagliptin, and gabapentin
Group B	5 patients	Metformin, glibenclamide, and gabapentin

Metformin 500 mg, sitagliptin 50 mg, glibenclamide 5 mg, and gabapentin 300 mg were administered to the patients selected.

Study Procedure

Evaluation of pharmacokinetic parameters will be carried out after the morning dose. A total of 8 blood samples (5 ml) taken from each participant at 0 h, ½ h, 1st h, 2nd h, 3rd h, 6th h, 12th h, and finally at 24th h. Vital sigthroughout the study. Blood samples were centrifuged at 3500 rpm for 15 min immediately after collection and transferred to glass containers where the samples kept frozen at −20°C. PK parameters such as AUC_{0-t}, AUC_{0-max}, C_{max}, and T_{max} are assayed for the two types of dosage regimen to determine the effectiveness of the treatment given.

Method Involved

LC/MS is the technique used in evaluating the pharmacokinetic parameters of gabapentin in DN patients along with two different dosage regimens. Typical LC-MS system is a combination of HPLC with MS using interfaces (ionization source). It is an analytical technique that coupled high-resolution chromatographic separation with sensitive and specific mass spectrum detection.[30] The sample is separated by LC, and the separated sample species are sprayed into the atmospheric pressure ion source, where they are converted into ions in the gas phase. The mass analyzer is then used to sort ions according to their mass-to-charge ratio and detector counts the ions emerging from the mass analyzer and may also amplify the signal generated from each ion. As a result, the mass spectrum (a plot of the ion signal as a function of the mass-to-charge ratio) is created, which is used to determine the isotopic nature of a sample, the masses of particles and molecules, and to elucidate the chemical structures of molecules.[31]

Patient Selection

Inclusion criteria

All DN patients with the good physical condition and above 21 years with a body mass index between 18.5 and 29.9 were selected. Gabapentin given for the first time in newly diagnosed DN patients were selected for the study.

Exclusion criteria

Patients using sitagliptin and glibenclamide more than 3 years were excluded. Patients on anti-tuberculosis therapy and with any other health abnormalities such as peripheral neuropathy, peripheral vascular disease, and retinopathy were excluded. Pregnant and nursing women and palliative patients were also excluded from the study.

Informed consent has been obtained from all the included patients. Patient confidentiality has been maintained throughout this study. The work has been approved by the Institutional Ethics Committee VISTAS-SPS/IEC/II/2018/06.

Statistical Analysis

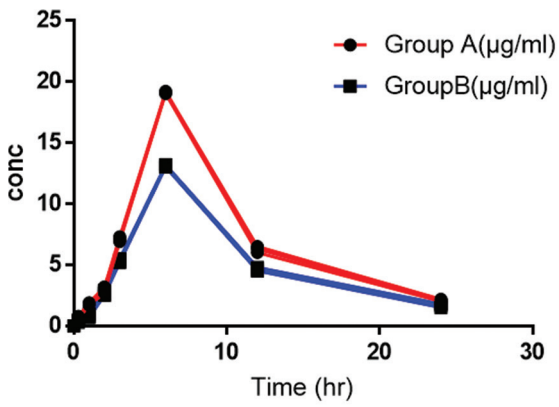
Correlation and regression analysis was carried out with a confidence interval of 95%, and $P < 0.05$ is considered statistically significant.

RESULTS

Baseline Parameters

It can be noticed from Table 1 that there are more diabetic patients among the age group of 18–35 years, and among 10 patients, more male (6) patients were participated in a study than female (4) patients.

Gabapentin Dose Concentration



Concentration versus time profiles of both the group patients analyzed after a single-dose oral administration of gabapentin 300 mg capsule.

Pharmacokinetic Parameters

From the Tables 2 and 3, we can infer that gabapentin at the dose of 300 mg shows an increase in pharmacokinetic parameters analyzed, i.e., AUC and peak plasma concentration of Group A when compared to Group B.

DISCUSSION

Co-administration of metformin and sitagliptin may lead to hypoglycemia followed by Lactic Acidosis.[32] Metformin and glibenclamide coadministration shows a greater incidence of hypoglycemia.[33] Both groups of drugs should be used with care, especially in elderly participants and those with impaired renal or hepatic function.

A study has shown that gabapentin well-tolerated, superior to placebo, and equivalent to amitriptyline with a short duration of the clinical trial in DN patients.[34] Hyperhomocysteinemia was an independent risk factor for the occurrence of DN. Treatment of existing hyperhomocysteinemia with folic acid and Vitamin B12 supplements may be useful in controlling the risk of microvascular complications in diabetes.[35] Actually, the therapeutic window of gabapentin was 2–20 µg/ml.[36] In our study, both group patients show an acceptable therapeutic range. However, when compared Group A patients with sitagliptin administration shows desirable therapeutic range without any serious adverse events. Glycemic control is important in diabetic to avoid neuropathic complications. By increasing the efficacy of the treatment, proper glycemic control can be achieved thereby rapid cure can be accomplished.

CONCLUSION

Diabetic neuropathic pain is common nowadays. Controlling blood glucose level is the key to bringing down the risk of diabetic nerve pain. Many medicines and other techniques are available to relieve the pain. In our study, sitagliptin shows an increase in AUC value and also increase in C_{max} and T_{max}. Hence, this may enhance increased therapeutic efficacy of the drug, and no serious adverse events were reported. Hence, this regimen may be pharmacokinetically superior to the regimen-containing glibenclamide.

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