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Review Article

A review of the drug pregabalin

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ABSTRACT

Pregabalin (PGB) is a well-established anticonvulsant and analgesic agent. The stydy reviewed the mechanism of action, pharmacokinetics, adverse drug reactions, contraindications, and various uses of PGB. Literature search was done to identify the relevant studies. PGB is an antagonist of voltage-gated calcium channels and specifically binds to α2-δ subunit to produce antiepileptic and analgesic activity. It has less protein binding activity and lacks hepatic metabolism. It is unlikely to cause pharmacokinetic drug-drug interactions. It has a wide safety margin and does not require serum drug monitoring. The above-mentioned favorable pharmacological benefits of PGB makes it a first-line or adjunctive therapy in various conditions like diabetic peripheral neuropathy, post-herpetic neuralgia, in partial seizures and generalized anxiety disorders.

Keywords: Pregabalin, Neuropathic pain, Partial seizures, Efficacy, Safety

INTRODUCTION

Pregabalin (PGB) is a well-recognized central nervous system depressant. It is a structural analog of gamma-aminobutyric acid. It is a non-opioid drug and is a α2-δ ligand that modulates the activity of voltage-gated calcium channels. It was introduced by US Food and Drug Administration (FDA) in December 2004. It was first discovered for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia (PHN). In June 2005, the drug was approved for the treatment of partial onset seizures with or without secondary generalization in adults as an adjunctive drug. Currently, FDA is considering the approval of PGB as an adjunctive therapy in adults with generalized anxiety disorder (GAD) or social anxiety disorder (SAD), spinal cord injury, and fibromyalgia. In the European Union, PGB is indicated for peripheral and central neuropathic pain, epilepsy, and GAD.[1]

Previous studies have shown that PGB can be used with safety and an acceptable efficacy in treatment of childhood refractory partial seizures.[2] Preclinical studies of PGB in animal models of neuropathic pain have shown its effectiveness in treating symptoms such as allodynia and hyperalgesia. Clinical studies in different age groups and in different types of neuropathic pain have projected it as the most effective agent either as monotherapy or in combination regimens. This is based on the cost effectiveness, tolerability and overall improvement in neuropathic pain scores.[3] Also, PGB is well-tolerated and relieves painful symptoms of distal symmetrical polyneuropathy (DPN) with minimal risk of dependence or impact on patient's diabetes control. PGB has consistently proved itself as an effective treatment for DPN and PHN in its extensive clinical trial programs. It is among the agents recommended by the American Academy of Neurology as a Group 1 treatment for PHN. European Federation of Neurological Societies have considered the drug as a first-line treatment for painful polyneuropathy.[4]

MECHANISM OF ACTION

PGB is an antagonist of voltage-gated calcium channels. It crosses the blood brain barrier and binds potently to

α2-δ subunit, an auxiliary protein associated with voltage-gated calcium channels. The drug binds to this channel thereby diminishing calcium entrance at hyperexcitable nerve terminals. This results in a decreased level of the excitatory neurotransmitters glutamate, norepinephrine, and substance P.[5] PGB reduces synaptic release of neurotransmitters in selected regions of the central nervous system including cortex, olfactory bulb, hypothalamus, amygdala, hippocampus, cerebellum, and dorsal horn of the spinal cord. This is achieved by binding of the drug to the α2-δ Type 1 protein of the P/Q type voltage-gated calcium channels thereby reducing the availability of calcium ions required for membrane fusion and exocytosis of neurotransmitters. This mechanism is responsible for the anxiolytic, anticonvulsant, and analgesic activity of PGB.[6]

PHARMACOKINETICS

PGB is administered orally. It is given in the dose range of 150-600 mg/day. In this dose range, the drug shows low inter-subject variability and rapid and extensive absorption approximately after 1 hr of oral intake. Also, absorption of the drug is proportional to its dose and steady state is achieved within 24-48 hrs following repeated administration.[2] one advantage is that the dosing regimen is not affected by food. PGB does not bind to plasma proteins. It is very less metabolized, <2%. It is not subject to hepatic metabolism and does not induce or inhibit liver enzymes such as the cytochrome p450 system. Therefore, it is unlikely to cause pharmacokinetic drug-drug interactions. It is excreted virtually unchanged by the kidneys. However, dose adjustment may be necessary in patients with renal insufficiency.[7]

DOSAGE RECOMMENDATIONS[3]

The various doses of PGB used in clinical disorders are shown in Table 1.

Table 1: Various doses of PGB used in clinical disorders.

Type of pain	Dose and duration
Diabetic painful neuropathy	150-600 mg/kg, 4-14 weeks
Chemotherapy-induced neuropathic pain	75-300 mg/day, 2-8 weeks
PHN	150-600 mg/day, 8-13 weeks
Fibromyalgia	150-600 mg/day, 4-12 weeks
Trigeminal neuralgia	150-600 mg/kg, 8 weeks
Post-operative pain	300-600 mg/day, pre/post-operatively

PHN: Post-herpetic neuralgia, PGB: Pregabalin

REVIEW OF EARLIER STUDIES FOR EFFICACY AND TOLERABILITY

An open label long-term study examining the safety and tolerability of PGB was conducted in Japanese patients with central neuropathic pain. This was a 53-week multi-centric open label trail of PGB at dose of 150-600 mg/day. PGB treatment improved total pain, sensory pain, and affective pain scores by visual analog scale (VAS). It also improved present pain intensity scores on short-form McGill pain questionnaire (SF-MPQ) and 10 items modified brief pain inventory (m-BPI-10) at end point compared with baseline. The mean changes from baseline in SF-MPQ VAS and m-BPI-10 scores at end point were −20.1 and −1.4, respectively. The treatment-related adverse effects were somnolence, weight gain, dizziness, and peripheral edema. Most adverse drug reactions (ADRs) were mild (89.1%) or moderate (9.2%) in intensity. The findings demonstrated that PGB is generally well-tolerated and provides a sustained efficacy over 53-week treatment period in patients with chronic central neuropathic pain.[8]

A randomized double-blind placebo (PL) controlled study was done by Mishra et al., in 2012 to evaluate the comparative clinical efficacy of amitriptyline, gabapentin, and PGB in neuropathic cancer pain. A total of 120 patients were enrolled in the study and divided into four groups. The groups were: Group AT-amitriptyline group, Group GB-gabapentin group, Group PG-Pregabalin, and Group PL-placebo. At the end of the study, there was significant decrease in pain score in Group PG as compared to other groups (Group AT [p=0.003], Group GB [p=0.042], Group PL [p=0.024]). The percentage of patients with lancinating pain and dysthesia were significantly less in Group PG than other groups. The results suggested that there was clinically significant morphine sparing effect of PGB. Also, the neuropathic symptoms were improved compared to other anti-neuropathic drugs in PG group.[9]

A study was done by Zaccara et al., in 2014 to assess the comparative efficacy and safety of PGB and levetiracetam for the reduction of seizure frequency in patients with partial seizures. It was a randomized double-blind, flexible-dose, parallel-group non-inferiority study of PGB and levetiracetam as adjunctive treatment in adult patients with refractory partial seizures. The study included a 6-week baseline phase, 4-week dose escalation phase, and 12-week maintenance phase. The proportion of patients with a >50% reduction in 28-day seizure rate was 0.59 (difference between groups [95% confidence interval], 0.00 [−0.08 −0.09]) with both PGB and levetiracetam. There was no significant difference between PGB and levetiracetam in percentage change in 28-day seizure rate (p=0.3571). In a *post-hoc* analysis, the proportion of patients who were seizure free for the maintenance phase was lower with PGB (8.4%) than with levetiracetam (16.2%, p=0.0155). The safety profiles of the study subjects were similar and consistent in both the groups. The results indicated that PGB is non-inferior and has a similar tolerability, to levetiracetam as adjunctive therapy in patients with partial seizures.[10]

A study was conducted by Dou et al., in 2014. It assessed the efficacy and safety of PGB in patients with neuropathic cancer pain undergoing morphine therapy. This was a double-blind randomized, PL controlled crossover study. A total of 40 cancer patients with severe neuropathic cancer pain were randomized into two groups: PGB-PL and PL-PGB. Patients in the PGB-PL group received PGB plus oral morphine in Phase I and PL plus oral morphine in Phase II. The treatment sequence for the PL-PGB group was PL plus oral morphine in Phase I and PGB plus oral morphine in Phase II. The primary outcome measure was the decrements in morphine dose; secondary outcomes included quantitative assessments of sleep, the constipation assessment scale and adverse effects. The mean minimal effective dose of morphine was significantly lower in the periods of PGB treatment than that of PL-controls ($p<0.001$). Compared with PL, PGB resulted in a significant sleep improvement as measured by sleep disturbance, sleep quantity, and sleep problems index ($p<0.001$), as well as a constipation assessment scale reduction ($p<0.001$). PGB resulted in a higher frequency of dry mouth and somnolence than PL ($p<0.05$). They concluded that PGB enhances the efficacy of oral morphine and reduces dose-related adverse reactions. The PGB-morphine combination is an effective approach in controlling neuropathic cancer pain.[11]

A study was conducted by Razazian et al., in 2014 to assess the efficacy and safety of PGB, venlafaxine, and carbamazepine in patients with painful diabetic neuropathy. It was a randomized double-blind parallel study. Two hundred and fifty-seven patients were randomized to receive carbamazepine, venlafaxine, and PGB. The primary outcome was subjective pain assessed by VAS. Secondary outcomes consisted of sleep, mood and work interference assessments, and a percentage of patients achieving at least 50% reduction in pain intensity. There was a significant difference in VAS scores from the baseline in all the groups. PGB was more efficacious than carbamazepine, and venlafaxine. There was an improvement in mean scores of sleep, mood, and work interference in all treatment groups. The study concluded that PGB was superior to carbamazepine, and venlafaxine in pain reduction in patients with diabetic neuropathy.[12]

A study was conducted by Moon et al., in 2010 to assess the efficacy and tolerability of PGB in Korean patients with peripheral neuropathic pain. It was a randomized double-blind, PL controlled multicenter study. Patients aged >18 years with neuropathic pain were enrolled in the study. They were randomly assigned to PGB (1500-600 mg/day) or matching PL. The primary endpoint was the difference in week 8 least squares mean daily pain rating scale (DPRS) score between PGB and PL. Secondary efficacy measures included the proportion of responders whose DPRS scores were reduced by >30% or >50% versus baseline, the daily interference scale, the Euro quality of life assessment, the medical outcomes study sleep scale, the hospital anxiety and depression scale, the patient global impression of change, and tolerability assessments. Adverse events were monitored. The mean DPRS score at the end point was significantly lower in the PGB group than in the PL group ($p=0.049$). In total, 26.1% of PGB treated patients reported >50% improvement in mean DPRS scores from baseline, compared with PL. Other secondary assessments also showed significant improvements. The main ADRs with PGB were dizziness (21%), somnolence (13.6%), face edema (6.2%), peripheral edema (6.2%), and weight gain (5.6%). The study concluded that PGB in the dose range 150-600 mg was associated with a significant reduction in mean DPRS score and generally good tolerability compared to PL in Korean patients with neuropathic pain.[13]

PUBLISHED ADRS

A study conducted by Onouchi et al., in 2014 demonstrated that the common adverse effects were somnolence in 50%, weight gain in 29%, dizziness in 23%, peripheral edema in 18%, feeling abnormal in 7%, constipation, thirst, and blurring of vision combined in 5%, asthenia, fatigue, hyperurecemia, nausea, neutropenia, and renal impairment combined in 3% of the subjects.[8]

Study conducted by Dou et al., in 2014 showed that PGB resulted in a higher frequency of dry mouth and somnolence than PL.[11]

Another study conducted by Toth, in 2014 showed that the most common ADRs seen with PGB occurring in at least 10% of any age group or dosage group are dizziness and somnolence. These ADRs increased with larger PGB doses. There were reports of dizziness in 31% of patients treated with PGB compared with 9% of those receiving PL. Somnolence is experienced in 22% of patients treated with PGB compared with 7% receiving PL. These ADRs occur when PGB is initiated and diminish after weeks of therapy with PGB. An abrupt discontinuation of PGB has uncommonly been linked to development of a syndrome similar to alcohol or benzodiazepine withdrawal. Hence, when PGB discontinuation is planned, a gradual tapering should occur.[14]

Another study conducted by Arnold et al., in 2011 showed that 9.9% of the subjects permanently discontinued the study participation due to treatment-emergent adverse effects. The most commonly reported ADRs were dizziness, somnolence, headache, peripheral edema, and increased weight. Most of the reported ADRs were mild to moderate with dizziness seen in 17.7%, and somnolence seen in 8% of the subjects.[15]

There are several case reports regarding the ADRs of PGB. In a study conducted by Kustermann et al., in 2014, a 20-year-old male patient was prescribed PGB 150 mg. The patient felt increasingly depressed. Later, he developed suicidal thoughts. These continued to worsen and led to a suicide attempt and the patient tried to poison himself to death.[16]

In another case report conducted by Smith et al., in 2008, a 35-year-old female patient developed extensive rash, induced by oral PGB (50 mg 3 times a day for neuropathy). The rash was diffuse, erythematous, and maculopapular rash localized to her back and extremities. PGB was discontinued, and the patient was treated with diphenhydramine and methylprednisolone. The rash almost completely resolved 1-week after PGB was discontinued.[17]

PRECAUTIONS AND CONTRAINDICATIONS

The doses of PGB must be adjusted in patients with renal insufficiency.[18]

ROLE IN THERAPY

PGB is the first drug to receive approved labeling from the FDA for the treatment of (i) painful diabetic neuropathy and PHN, (ii) as an adjunctive therapy for adults patients with partial onset seizures,[19] (iii) treatment of peripheral and central neuropathic pain in adults,[20] (iv) as adjunctive therapy in adults with GAD or SAD.[1]

PGB is a new anxiolytic that has been licensed for the treatment of (i) GAD, (ii) central and peripheral neuropathic pain (iii) neuropathic pain associated with diabetic peripheral neuropathy and PHN, (iv) partial onset seizures in (v) treating psychic and somatic symptoms of GAD and (vi) in subsyndromal depressive symptoms of GAD in Europe.[21]

Studies have demonstrated that premedication with PGB is effective for the prevention of post-operative pain in patients after coronary artery bypass grafting.[22]

CONCLUSION

PGB is a well-established anticonvulsant, analgesic, and anxiolytic agents. It is approved for the treatment of painful diabetic neuropathy, PHN, peripheral, and central neuropathic pain, as adjunctive therapy in adults with GAD and partial onset seizures. The advantages of PGB are its minimal protein binding, lack of hepatic metabolism, and minimal drug interactions. The main ADRs of the drug are somnolence, dizziness, and weight gain. PGB has shown efficacy and is approved as a monotherapy for painful diabetic neuropathy although several guidelines recommend combination therapy for challenging cases. At present, very few studies are available on monotherapy of PGB. However, the decision of monotherapy versus combination therapy should be at the physician's discretion.

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