Pregabalin: a new drug for epilepsy, neuropathic pain and anxiety

Dr. Patrick Kwan
MRCP, PhD, FHKCP, FHKAM (Medicine)

Prince of Wales Hospital
Associate Consultant, Honorary Associate Professor, Division of Neurology,
Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Introduction

Epilepsy affects up to 1% of the population. Despite antiepileptic drug (AED) treatment, up to one third of patients continue to experience seizures. Pregabalin (PGB) is the latest compound that joins the list of approved “new” AEDs. In addition to epilepsy, it has demonstrated efficacy for the treatment of neuropathic pain and generalised anxiety disorder.

Mechanism of Action

PGB [(S)-3-(aminomethyl)-5-methylhexanoic acid] (Figure) is licensed under the trade name Lyrica. Similar to its predecessor gabapentin but with greater potency, PGB binds to the alpha-2-delta subunit site of neuronal voltage-gated calcium channel, resulting in reduced depolarisation-induced calcium influx at nerve terminals with a consequential reduction in the release of excitatory neurotransmitters.

Pharmacokinetics

PGB has a favourable pharmacokinetic profile (Table). It is rapidly and extensively absorbed after oral dosing in the fasted state. Administration of PGB with food has no clinically relevant effect on the amount of PGB absorbed although the rate of absorption may be decreased. Maximal plasma concentration is reached 1 hour after single or multiple doses and steady state is achieved within 24 to 48 hours after repeated administration. The oral availability of PGB is high at >90% and is independent of dose. The maximal plasma PGB concentration and total exposures are proportional to dose after multiple dosing. Routine monitoring of plasma concentrations of PGB is not necessary.

The mean elimination half-life of PGB is 6.3 hour. PGB undergoes negligible metabolism in humans and is excreted virtually unchanged by the kidneys. Because of this, dose reduction in patients with impaired renal function is needed. PGB does not bind to plasma proteins. It is not subject to hepatic metabolism and does not induce or inhibit liver enzymes such as the cytochrome P450 system. Consequently, PGB has very low potential for pharmacokinetic drug-drug interactions, which is a particular advantage for its use in patients receiving other AEDs or non-AEDs.

Efficacy

Adjunctive Treatment of Epilepsy

PGB has been evaluated in three pivotal fixed-dose randomised, double-blind, placebo-controlled, multicentre trials involving patients at least 12 years of age with refractory partial seizures. To enter the trials, patients must have failed at least one or two previous AEDs and must be on one to three concurrent AEDs. After a 6- or 8-week baseline phase, patients enter a 12-week double blind treatment phase.

In the largest trial conducted in the US and Canada, 453 patients were enrolled. Patients were randomly assigned to placebo, PGB 50, 150, 300 or 600 mg,6 administered twice daily. Seizure frequency reduction from baseline for was 7%, 12%, 34%, 44% and 54%, respectively. In the second trial conducted in Europe, South Africa and Australia, 287 patients were randomised to placebo, PGB 150 or 600 mg,6 given three times daily. Both doses of PGB were significantly more effective than placebo in reducing seizure frequency and had higher responder rates (defined as reduction in seizure frequency of 50% or more). In the third trial involving 312 patients recruited from centres in US and Canada, patients were randomised to receive placebo or one of two regimens of 600 mg/d PGB as two or three divided doses. Both regimens were similarly effective in reducing seizure frequency (twice daily, 44%; thrice daily, 53%; placebo, 1% increase). A separate ad hoc analysis on an intent-to-treat (ITT) patient population showed that PGB doses of 300 or 600 mg,d were able to achieve complete freedom from seizure in 7% and 19% of patients respectively over a 12-week period. Considering the refractory nature of the trial patients, the efficacy data may be viewed as highly encouraging.

In summary, data from these pivotal trials demonstrate that PGB doses in the range 150 to 600 mg,d, administered two or three times daily, are effective as adjunctive therapy for partial-onset seizures.

Painful Diabetic Peripheral Neuropathy

An estimated 24% of the diabetic population may suffer from painful diabetic neuropathy (DPN). Both patients with type I and type II diabetes mellitus are affected. There have been five therapeutic trials of PGB on patients with DPN. In these studies, patients aged 18 years or older with a diagnosis of DPN for more than 6 months were considered eligible if they had a minimum baseline daily score of 4 on an 11-point numerical pain scale, and had pain equal to 40 mm on the 100-mm visual analogue scale (VAS) of the short-form McGill Pain Questionnaire (SF-MPQ). Duration of treatment in these trials ranged from 5 to 12 weeks. Significant reduction in pain was noted in patients randomised to PGB 300 mg or 600 mg,d. In addition, they had significantly less sleep disturbance and better quality of life scores compared with the placebo group.
Postherpetic Neuralgia

Postherpetic neuralgia (PHN) occurs at a defined period after rash onset or healing of herpes zoster infection. The condition can be debilitating and the risk is particularly high with advancing age. There has been three randomised, double-blind, placebo-controlled, multicentre studies of PGB for the treatment of PHN.12-14 The inclusion criteria were similar to those in the DPN trials. PGB 150 to 600 mg/day was superior to placebo in relieving pain associated with PHN and such improvements were sustained through 8 to 13 weeks’ treatment duration in all three studies. Patients in the PGB groups also had significantly reduced sleep interference scores and improvements in health-related quality of life scores.

Generalised Anxiety Disorder

Although benzodiazepines have been the mainstay of treatment for generalised anxiety disorder (GAD), their propensity to cause dependence has called for the development of newer agents. PGB has been evaluated for this indication in three clinical trials.15-17 These trials entailed patients 18 years or older diagnosed to have GAD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Treatment duration ranged from 4 to 6 weeks. PGB in doses of 150 to 600 mg/day was found to be an effective agent in the short-term treatment of GAD as demonstrated by improvement in the Hamilton Anxiety Rating Scale compared with placebo.

Safety and Tolerability

PGB is generally well tolerated. Combining data from all the controlled trials, the discontinuation rate due to adverse events was 13% for patients taking PGB and 7% for those receiving placebo.18 The most common adverse reactions were dizziness (28.9% vs. 8.9% for placebo) and somnolence (23.7% vs. 8.8% for placebo). Other notable central nervous system side effects include paraesthesia and ataxia. Non-CNS side effects considered common include peripheral oedema and weight gain, although they rarely (<1%) directly led to discontinuation of PGB. There is currently no data available on the safety of PGB during pregnancy.

Approval Status

PGB has been approved as add-on therapy in adults for partial seizures with or without secondary generalisation, and for the treatment of neuropathic pain (specifically DPN and PHN in the US, peripheral neuropathic pain in Europe and Hong Kong, no specific pain syndromes in Australia). PGB is undergoing registration in a growing number of countries. Application for its use in GAD is currently under review by the US and European regulatory authorities. PGB is also being evaluated for other conditions, such as fibromyalgia.

Conclusions

PGB is an effective and well-tolerated novel oral therapy for epilepsy, neuropathic pain and GAD. It has so far received approval for the treatment of the first two conditions. Effective doses appear to range from 150 to 600 mg/day. With its good efficacy and tolerability, favourable pharmacokinetic profile and low risk of drug–drug interactions, PGB is a welcomed addition to the armamentarium for the treatment of these common disorders. It is hoped that accumulated experience will further optimise its use so that more patients can lead safer and more fulfilling lives.

References


Figure. Chemical structure of pregabalin.

Table. Clinical pharmacological profile of pregabalin

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<th>Mechanism of action</th>
<th>Binding to alpha-2-delta subunit on voltage-gated calcium channels</th>
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<td>Tmax</td>
<td>1 hour</td>
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<tr>
<td>Bioavailability</td>
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