Pregabalin

R Chunder

Corresponding author, email: reshmachunder@yahoo.com

Abstract

Pregabalin is a newer generation gabapentinoid and is structurally similar to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Gabapentin was initially synthesised over forty years ago as an adjuvant antiepileptic drug but has since become widely prescribed to treat neuropathic pain. Similarly, pregabalin use in epilepsy is limited and its use has been targeted for the treatment of neuropathic pain.[1,2]

S Afr Pharm J 2022;89(2):16-19

Indications

Pregabalin is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy, fibromyalgia, post-herpetic neuralgia, neuropathic pain associated with spinal cord injury, and as adjunctive therapy for the treatment of partial-onset seizures in patients one month of age and older.[1]

Pregabalin has FDA approval for the treatment of peripheral neuropathic pain, generalised anxiety disorder and as an adjunct therapy for epilepsy.[3]

In South Africa, pregabalin is registered for post-herpetic neuralgia and painful diabetic polyneuropathy in adults.[4]

Neuropathic pain is an unpleasant emotional and sensory experience that can have a major impact on a person's general health, social and economic wellbeing, psychological health and overall quality of life. It is defined by the International Association for the Study of Pain (IASP 2011) as "pain caused by a lesion or disease of the somatosensory nervous system." Neuropathic pain is classified as central or peripheral:[5]

- Central neuropathic pain is caused by a disease or lesion of the central somatosensory nervous system.
- Peripheral neuropathic pain is caused by a disease or lesion of the peripheral somatosensory nervous system.

Common symptoms of neuropathic pain description include the following:[4,5]

- Burning feeling
- Tingling sensation
- Electric shock
- Numbness
- Itching
- Prickling
- Pins and needles sensation
- Hyperalgesia (increased response to a normally painful stimulus)
- Anaesthesia dolorosa (pain felt in an anaesthetic region)
- Allodynia (pain caused by a stimulus that does not normally provoke pain

Pharmacokinetics

The pharmacokinetic parameter profile of pregabalin is similar to many psychotropic drugs.[6-9]

Absorption – rapidly and extensively absorbed with plasma peak concentration within 1.5 hours after administration and plasma concentration increases proportionately with increasing dose.[6,7] The absolute bioavailability remains constant at approximately 90% irrespective of dosage. Food decreases the rate of absorption resulting in lower and delayed maximum plasma concentration but does not affect the extent of absorption. Therefore, pregabalin can be administered without regard to meals.[6-9]

Metabolism – pregabalin undergoes negligible metabolism. It is not metabolised by nor does it inhibit hepatic enzymes that are responsible for the metabolism of other drugs.[6-9]

Elimination – pregabalin is more than 90% eliminated by renal excretion as unchanged drug, with an elimination half-life of approximately 6 hours. Steady-state is reached within two days of regular dosing.[6-9]

Pharmacodynamics

Pregabalin has a similar structure to gamma-aminobutyric acid (GABA) but does not bind to the GABA receptors. Instead, pregabalin exerts its effects by binding to the alpha2-delta subunit of voltage-dependent calcium channels in the central nervous system (CNS).[6,7] Pregabalin does not modulate cyclooxygenase activity, serotonin receptors, opiate receptors, dopamine receptors or sodium channels. Another contributing factor to the mechanism of action of pregabalin is that it prevents the alpha2-delta subunit from being attached from the dorsal root ganglia to the spinal dorsal horn.[1,3]

Mechanism of action

Pregabalin modulates the release of several excitatory neurotransmitters such as substance-P, glutamate, norepinephrine and calcitonin gene-related peptide, by binding pre-synaptically to the alpha2-delta subunit of voltage-gated calcium channels in the CNS.[1,10]

Pregabalin does not interact with either $GABA_A$ or $GABA_B$ receptors. It is also not converted metabolically into GABA or a GABA agonist, nor is it an inhibitor of GABA uptake or degradation.[4]

Dosage

The recommended starting dose of pregabalin is 75 mg twice daily with or without food. The dose may be increased to 150 mg twice daily after three to seven days based on individual patient tolerability and response.[4]

Refer to Table I for dosage and adjustments in special population groups. Also refer to Table II for pregabalin dosage adjustment for renal impairment.

Table I: Dosage and adjustments in special population groups[4,11,12]

Patient group	Dosage and adjustments
Use in patients under 18 years	The safety and effectiveness of pregabalin in patients with neuropathic pain under 18 years of age have not been established.
Use in the elderly (> 65 years of age)	No dosage adjustment is required for elderly patients unless they have compromised renal function.
Use in patients with hepatic impairment	No dosage adjustment is necessary for patients with hepatic impairment.
Use in patients with renal impairment	Pregabalin undergoes renal excretion from systemic circulation as an unchanged drug. Dosage reduction is required in patients with compromised renal function as the clearance is directly proportional to creatinine clearance. Refer to Table II.
Patients receiving haemodialysis	The pregabalin dose should be adjusted according to the renal function. A supplementary dose should be given immediately after every 4-hour haemodialysis treatment, in addition to the daily dose. Refer to Table II.

Table II: Pregabalin dosage adjustment for renal impairment[4,11,12]

Creatinine clearance (CL_{CR}) (ml/min)	Starting dose	Maximum dose (mg/day)
≥ 60	150 mg twice daily	300 mg twice daily
30–60	75 mg once or twice daily	150 mg once or twice daily
15–30	25–50 mg once or twice daily	75 mg once or twice daily
< 15	25 mg once daily	25–50 mg once daily
Supplementary dose after every 4-hour haemodialysis	25 mg as a single dose	50 mg as a single dose

Pregabalin in diabetic peripheral neuropathy

Chronically elevated high blood sugar levels in type II diabetics cause nerve damage resulting in diabetic peripheral neuropathy.

Nerve damage occurs from microvascular damage to blood vessels supply nerves. Pregabalin is an effective treatment for the symptoms of diabetic peripheral neuropathy, with a recommended dose of 300–600 mg daily. Pregabalin suppresses the activity of the excitatory primary afferent fibres that carry nociceptive information to the spinal dorsal horn.[3]

Pregabalin in postherpetic neuralgia

Herpes zoster occurs when the Varicellar zoster virus that causes chickenpox is reactivated from its latent state up to decades later. Herpes zoster manifests as a painful rash commonly known as shingles. The virus can be treated with antivirals, but the painful sensation following the attack can persist for months or years without the continuing rash. Almost 20% of those suffering from herpes zoster develop post-herpetic neuralgia due to the damage of nerve fibres from the inflammatory response accompanying the reactivation of the Varicellar zoster virus.[3]

The gabapentinoids are first-line treatment with pregabalin having preference to gabapentin at one-sixth of the dose. The recommended dose of 150–600 mg daily shows consistent improvement in pain scores in patients with post-herpetic neuralgia.[3]

Pregabalin in neuropathic pain associated with spinal cord injury

Neuropathic pain is reported in almost two-thirds of patients that have motor and sensory deficits following an injury to the spinal cord. Pregabalin has been shown to be effective in treating patients with neuropathic pain associated with spinal cord injury. Pregabalin also improves anxiety, sleep and general patient well-being in these patients. A recent study by Sun et al. has shown that gabapentinoids promote regeneration of corticospinal axons in mice subsequent to spinal cord injury.[13]

Pregabalin also augments myelin repair in rat models, which may contribute to its effectiveness in treating damage caused by spinal cord injury.[3]

Withdrawal symptoms

Abrupt discontinuation of pregabalin treatment can result in withdrawal symptoms in some patients. These symptoms include nausea, sweating, insomnia, diarrhoea, headache and anxiety.[6,12]

Therefore, it is recommended that patients undergo a taper period of about one week when treatment needs to be discontinued.[4,6,12]

Safety profile

Studies have shown that the adverse effect profile of pregabalin is well tolerated. The majority of the adverse events experienced in premarketing clinical studies or post-release studies are mild to moderate in severity. The most common adverse events seen in trials are dizziness and somnolence, the incidence of which is dose related.[2,4]

Other possible adverse events include euphoria, gait imbalance, visual blurring and cognitive difficulties. Possible systemic effects include dry mouth, weight gain, increased appetite, peripheral oedema, infection and constipation.[2,4]

Special precautions

Patients are recommended not to drive or operate complex machinery or engage in other potentially hazardous activities as pregabalin often causes somnolence and dizziness. Patients with glucose-galactose malabsorption, Lapp lactase deficiency or galactose deficiency should not take pregabalin. There have been rare post-marketing reports of hypersensitivity reactions such as urticaria and angioedema.[4,12]

Special precaution needs to be taken for the following patients:[4]

- Renal impairment
- Substance abuse
- Patients with cardiovascular disease (including heart failure)
- History of angioedema

Patients should be monitored for signs of suicidal ideation and behaviour.[4,12]

Pregnancy and lactation

Pregabalin should not be used during pregnancy as animal studies have shown reproductive toxicity and the potential risk to humans is unknown. Pregabalin is excreted in the milk of rats but it is not known if pregabalin is excreted in breast milk of humans. Therefore, pregabalin is not recommended for use during pregnancy and lactation.[2,12]

Interactions

Pregabalin may cause additive CNS depressant effects with opiates (e.g. oxycodone) and benzodiazepines (e.g. lorazepam). The risk of angioedema with ACE inhibitors may also be increased.

Pregabalin may also augment the CNS depressant effects of alcohol.[1,4,12]

References

1. Pregabalin: Uses, Interactions, Mechanisms of Action. Drugbank Online. Available from: https://go.drugbank.com/drugs.
2. Toth C. Pregabalin: latest safety evidence and clinical implications for the management of neuropathic pain. Ther Adv Drug Saf. 2014;5(1):38-56. https://doi.org/10.1177/2042098613505614.
3. Alles SRA, Cain SM, Snutch TP. Pregabalin as a pain therapeutic: Beyond calcium channels. Front Cell Neurosci. 2020;14:83. https://doi.org/10.3389/fncel.2020.00083.
4. Pfizer Laboratories (Pty) Ltd Lyrica. Final approved PI - 15 May 2015. Available from: https://www.sahpra.org.
5. NICE guideline. Neuropathic pain in adults: pharmacological management in non-specialist settings. 2013. Available from: https://www.nice.org.uk.
6. WHO Expert Committee on Drug Dependence. Pregabalin Pre-review Report. 2017. Available from: https://www.who.int.
7. Schulze-Bonhage A. Pharmacokinetic and pharmacodynamic profile of pregabalin and its role in the treatment of epilepsy. Expert Opin Drug Metab Toxicol. 2013;9(1):105-15. https://doi.org/10.1517/17425255.2013.749239.
8. Bockbrader HN, Wesche D, Miller R, et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet. 2010;49(10):661-9. https://doi.org/10.2165/11536200-000000000-00000.
9. Bockbrader HN, Radulovic LL, Posvar EL, et al. Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol. 2010;50(8):941-50. https://doi.org/10.1177/0091270009352087.
10. Rajappa GC, Vig S, Bevanaguddaiah Y, Anadaswamy TC. Efficacy of pregabalin as premedication for post-operative analgesia in vaginal hysterectomy. Anesth Pain Med. 2016;6(3):e34591. https://doi.org/10.5812/aapm.34591.
11. MIMS. Pregabalin. Available from: https://www.mims.com.
12. Lyrica 25mg hard capsules. Summary of product characteristics. Mar 2022. Available from: https://www.medicines.org.uk.
13. Sun W, Larson MJE, Kiyoshi CM, et al. Gabapentinoid treatment promotes corticospinal plasticity and regeneration following murine spinal cord injury. J Clin Invest. 2020;130(1):345-58. https://doi.org/10.1172/jci130391.