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Review Article

A review on pregabalin for the treatment of painful diabetic peripheral neuropathy

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ABSTRACT

Pregabalin is an anti-epileptic drug which has been used for the treatment of diabetic peripheral neuropathy. Earlier, it was more prescribed as an adjuvant therapy for treating the partial seizures with or without secondary generalization in adults. It is an antagonist of voltage sensitive calcium ion channel on the presynaptic neuron. Pregabalin has a very good pharmacokinetic profile, possesses linear pharmacokinetics with low inter-variability of subjects. It does not show protein binding and does not interfere with the metabolism of other drugs because pregabalin undergoes very less metabolism. This factor has confirmedly shown that its benefits outweigh the risk. Different clinical trials and case reports have confirmed the fact that is reduces the pain involved in peripheral neuropathy. Though, more drugs have come like tricyclic antidepressant to manage the pain but due to their adverse effects, they are less used. This reappraisal is all about the pregabalin, its role, and where it stands among other drugs for management of pain aassociaed with diabetic peripheral neuropathy.

Keywords: Carbamazepine, Desipramine, Neuropathy, Pregabalin, Seizures

INTRODUCTION

The drug pregabalin is being used for over a decade and is a U.S. FDA (Food and Drug Administration) approved drug to lessen the pain associated with diabetic peripheral neuropathy. Pregabalin is not only used for diabetic peripheral neuropathy but also used for the treatment of pain associated with post herpetic neuralgia, spinal cord injury, and fibromyalgia. This review article is concerned with only diabetic peripheral neuropathy; its pathophysiology and its treatment by pregabalin. The pregabalin like gabapentin acts on the α2-δ Type 1 subunit of voltage gated calcium channel present on the presynaptic neuron. The diabetic peripheral neuropathy is a polyneuropathy involving different areas of the body and is more serious than mononeuropathy.[1] About 4 to 6 % of the population is affected by neuropathic pain and the worst part is that it can be managed and not cured. The drugs which are used for the management of peripheral neuropathy in diabetes are many but of all, pregabalin has excelled. The pharmacokinetic profile of pregabalin is excellent and is a boon for diabetic people who also take

other drugs. Pregabalin does not show protein binding and undergoes very little metabolism. So, there is very fewer drug interactions and does not interfere with the metabolism of other drugs. The adverse drug effects are milder and usually discontinuation of a drug is not required. This article encompasses all the aspects of pregabalin and proves that why pregabalin is becoming a drug that is mostly prescribed around the world for the treatment of Diabetic Peripheral Neuropathy.[2]

PATHOPHYSIOLOGY OF DIABETIC PERIPHERAL NEUROPATHY

The term "diabetic peripheral neuropathy" is a combined term originating from peripheral neuropathy and diabetes. So, this disease is a complication due to diabetes. DPN (Diabetic Neuropathy is a kind of polyneuropathy in which different areas of the body get affected and is more serious than mononeuropathy. This term peripheral neuropathy is often used to refer polyneuropathy and as the name suggests, peripheral, the peripheral nerves are involved and get damaged. The three peripheral nerves which get damaged are sensory nerves, motor nerves, and autonomic nerves.[3] It is important to know that any one nerve group or all can be affected simultaneously. Burning sensation, numbness, needles pain in feet and hands are the symptoms of DPN.

Neuropathic pain is a disorder which has impacted 4% to 6% of the population.[4] There are different complications which are very well associated with diabetes and they develop gradually over the time. Instances include cardiovascular diseases, neuropathy, nephropathy, retinopathy, foot damage, etc. Peripheral neuropathy is the most common and prevalent in diabetic people.[5] The findings state that distal and sensory nerve degeneration, axonal loss and peripheral nerve endoneurial microangiopathy exist in these people. This affects the proper functioning of peripheral nerves and in this condition; they may send the signals of pain or sensations like burning or other even if there is no such kind of stimulus. Metabolic disorders are the main cause of this disease. Of all the factors that are attributable to the development of this disease, polyol pathway hyperactivity (popularly called as polyol pathway theory) is the most acceptable and recognized. This pathway converts the glucose into fructose via the production of sorbitol. When hyperglycemia occurs, more and more glucose is available for the conversion of glucose into sorbitol; thereby increasing the consumption of NADPH (Nicotinamide Adenine dinucleotide phosphate). As we know, this cofactor is needed while converting glucose to sorbitol by aldose reductase.

Low NADPH levels lead to decreased level of nitric oxide and glutathione According to different articles, glutathione seems to be the primary cause of oxidative stress. Oxidative stress represents the heavy production of reactive oxygen species (ROS) in the cell and damage by these reactive intermediates manifest as neuropathy in diabetes. Glutathione is an excellent scavenging agent of these toxic species, which gets depleted in diabetes. [6] Polyol pathway is given in Figure 1.

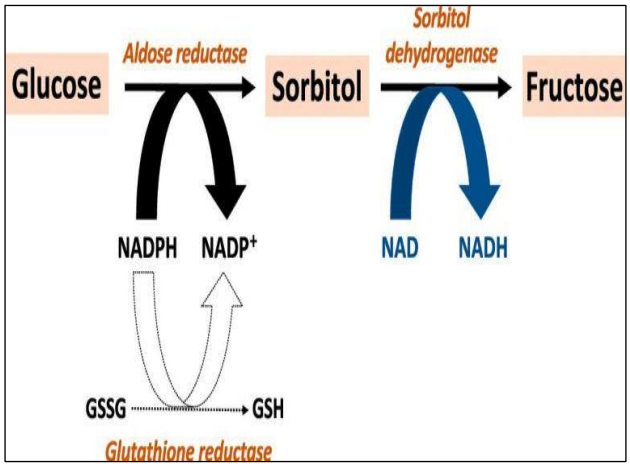

Figure 1: Polyol pathway leading to the formation of Sorbitol which leads to diabetic complications.[19]

PREGABALIN EFFICACY AND EFFECTIVENESS

This drug has not been given the proper recognition which it should have been given. It may be due to unawareness among the physicians or due to the wrong conception about the drug. The drug should be taken for a longer duration in diabetic people with caution. Most people do not respond to the drug when it is given for a short period of time and with the low dose. The dose required for clinical efficacy is between 300 to 600mg/day.[7] This dose should be continued for at least 3 weeks, and if the person is not responding, then, other drugs or treatments should be tried.[8] Well, a large number of clinical studies have been done to support the potential of pain relieving attribute of pregabalin.

There are a series of case reports of pregabalin telling the effectiveness of pregabalin to reduce the pain. Pregabalin has shown more benefits in the treatment of DBN than as an adjuvant therapy for the treating epilepsy.[9]

After the publication of different randomised controlled clinical trials, the use of pregabalin for the treatment of neuropathy came into the mainstream despite being off label. It got approved for neuropathic pain management in the year 2004 within the United States of America and Europe and then it got many other indications for various neuropathic pain conditions.[10] Now, among all the treatments available for diabetic peripheral neuropathy, gabapentinoids like pregabalin are considered to be the first-line treatment. In North America alone, pregabalin is used for the management of neuropathic pain associated with postherpetic neuralgia, diabetic peripheral neuropathy, and fibromyalgia. The only approved treatment for central neuropathy in Europe is Pregabalin besides the indication for generalized anxiety disorder.[11]

DOSAGE OF PREGABALIN

The major route of excretion of this drug is from the kidneys through urine. So, in the diabetic people with renal impairment, care should be taken while administration. The starting dose may vary from individual to individual but the general dosing is 75mg orally every night at bedtime or 75mg orally two times a day.[12] The dose is gradually increased to an oral dose of 150 mg twice daily. In most patients, it has been found that a dose range from 300 to 600 mg/day gives an optimum result. However, more than this dose may prove to be intolerable. If pain relief is scant after 2 to 4 weeks with 300 to 400mg/day or if there is intolerability with this dose range, then a patient is advised to discontinue the drug.[13]

WHY THE PREGABALIN IS BETTER THAN OTHER DRUGS FOR THE TREATMENT OF DPN?

According to the University of Chicago's Center for Peripheral Neuropathy (UCCPN), 60% of people suffering from diabetes have some kind of nerve disorder.[14] The reason that is attributed to this neuropathy is the high level of sugar in the blood. The cure of this complication does not exist. This very complication can only be managed by various drugs. The pain relieving medications due to nerve damage include tricyclic antidepressants such as desipramine, amitriptyline, and imipramine. They can provide relief from mild to moderate pain by interfering with the chemical processes in the brain.[15] They also cause a number of side effects like sweating, weight gain, dizziness and constipation, cardiac arrhythmia in patients with ischemic heart disease. Amitriptyline is dangerous in particular in this regard. As the diabetic people have some sort of cardiac disease as a complication, so, tricyclic antidepressant should be used cautiously.[16] Shreds of evidence are there that tell carbamazepine which is an anti-epileptic drug is not an analgesic but less often used for the treatment of symptomatic diabetic sensory polyneuropathy. Lidocaine patches are available for the people to reduce the pain associated with diabetic neuropathy. Similarly, mexiletine is also used for relieving pain caused by peripheral neuropathy. Capsaicin is a chemical substance obtained from cayenne peppers. This substance is available as a cream in the market for treating the pain. It is directly applied on the skin over the affected area.

Apart from all these, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, ibuprofen, acetaminophen, and naproxen are also very commonly prescribed.[17] The most important thing while taking these types of medications is to be careful about the side effects of these medications, especially the alteration of the kidney function in diabetic people. All the above medications have proved to be useful for treating the mild to moderate pain but not the severe pain.[18] To treat severe pain, the drugs which are prescribed are narcotic pain relievers like oxycodone, codeine, fentanyl, etc. Most of the narcotic pain relievers cause respiratory depression, urinary retention, and, blurring of vision, and this can be troublesome for the elderly people suffering from DPN and already having different others complications. Pregabalin is not associated with these kinds of adverse drug reactions of other drugs. Moreover, it is free from protein binding and has very less metabolism. This proves to be fruitful for the diabetic people who mostly are on the other drugs alongside. So, from the above, it can be inferred why the pregabalin is gaining more popularity and excelling over other drugs.

INDICATIONS

Pregabalin is a synthetic amino acid compound that is commonly used for the treatment of pain associated with post herpetic neuralgia, spinal cord injury, diabetic peripheral neuropathy, and fibromyalgia.

Pregabalin is also used as an adjunctive therapy to treat partial seizures with or without secondary generalization in adults.

MECHANISM OF ACTION

The exact mechanism by which pregabalin shows the effect is not yet completely understood. However, different clinical studies including the structure activity analysis of molecules that bind with alpha 2 - delta subunit and decreased activity of the drug in mice having the mutation in the α2-δ Type 1 in the CNS region suggest that it acts by binding to the alpha2 delta receptor Type 1. The α2-δ Type 1 is an auxiliary subunit of voltage sensitive calcium channel. Whenever this subunit is modulated by the pregabalin, entry of calcium ions into the presynaptic neuron decreases and due to this, the neurotransmitter glutamate release gets decreased and hence, the neuronal excitability of postsynaptic neuron decreases.

PHARMACOKINETICS OF PREGABALIN

A clinical study including a total of 472 subjects was done to assess the single, and multiple doses tolerance studies. Single dose tolerance studies involved dose ranging from 1mg to 300mg and multiple dose tolerance studies involved 25mg, 100mg, 200mg, 300mg doses after every 8 hours and 300 mg every 12 hours for two weeks. Other studies were bioavailability study, C mass balance, and metabolic study.[14] Data from all these studies suggest that pregabalin possesses linear pharmacokinetics with low inter-variability of subjects.

After the oral administration, pregabalin gets rapidly absorbed. Maximum plasma concentration C_{max} is achieved after 1 hour of administration. Steady state concentration is achieved within 24 to 48 hours after repeated dose. The oral bioavailability of pregabalin is high that is 90% approximately and found to be independent of dose administration. The mean elimination half life of pregabalin is 6.3 hours and is independent of dose and frequency of administration.

The extent of drug absorption is not affected by food but the time taken for attaining the maximum plasma concentration is increased.

The system L- amino acid is the major transporter by which pregabalin is transported across the gut and brain. The same system is also responsible for transporting of large amino acids. It crosses the blood brain barrier (BBB) and therefore, shows the CNS activity. The metabolism of pregabalin is very less and is excreted unchanged from the kidney via urine. The major metabolite that has been found is N-methyl pregabalin. Plasma protein binding is also negligible. It does not induce or inhibit the hepatic enzymes such as CYP450 enzymes.[20] The apparent volume of distribution of pregabalin following the oral administration is approximately 0.5L/kg. The renal clearance of pregabalin is 72ml/min. Pregabalin is not prone to or cause severe drug-drug interactions and this feature has been found useful in the treatment of patients with suffering from epilepsy, who are already on different other drug therapies like the patient of refractory epilepsy. As the major route of excretion of pregabalin is through the kidney, thus, dose reduction is needed in the patients with impaired renal function or when the creatinine clearance is less than 60ml/min.

ADVERSE EFFECTS ASSOCIATED WITH PREGABALIN

Pregabalin is an anticonvulsant drug and is particularly used for the treatment of neuropathic pain like diabetic neuropathic pain, postherpetic neuropathic pain, CRPS (complex regional pain syndrome), partial onset seizure and fibromyalgia.

In a clinical trial, 14% of patients who were treated with pregabalin and 7% of patients treated with placebo discontinued the treatment prematurely due to adverse drug reactions. The experimental group who discontinued the drug suffered from dizziness and somnolence, and the same reason was with the placebo treated group. Other adverse drug reactions that were responsible for the discontinuation of therapy was blurred vision, confusion, asthenia, ataxia, and abnormal thinking. Major and minor adverse effects are given in Table 1.

INTERACTIONS WITH OTHER DRUGS

Pharmacokinetic properties indicated that it has the low potential to cause drug-drug interaction as it is not metabolized and does not affect the cytochrome P450 system. It does not bind to the plasma proteins significantly. However, there exist some interactions, the knowledge of which is important.[21]

Propoxyphene

When both drugs are co-administered in the patients with neuropathy, then, some people experience difficulty in thinking, confusion, dizziness, difficulty in concentration, and drowsiness.

Table 1: Major and minor adverse effects of pregabalin.[4]

Major adverse drug effects	Minor adverse drug effects
Chills	Bloating or swelling of the face, arms, and hands
Cough	Blurred Vision
Diarrhea	Burning, tingling, numbness or pain in the hands, arms, feet, or legs
Difficulty with swallowing	Walking and balance changes
Dizziness	Clumsiness
Fast heartbeat	Confusion
Hives	Delusions Dementia Difficulty in having a bowel movement (stool)
Itching	Difficulty in speaking
Skin rash	Double vision
Sore throat	Dry mouth
Sores	Fever
Weakness	Headache
Difficult or labored breathing	Hoarseness
Shortness of breath	Eye disorder
Tightness in the chest	False or unusual sense of well-being

Buprenorphine

The concomitant use of buprenorphine with pregabalin in the patients with the diabetic neuropathic pain, showed increased buprenorphine concentration and respiratory depression. The mechanism of action underlying involves some degree of additive pharmacological effect.

Sodium oxylate

This drug is the shortened form of sodium γ - hydroxybutyrate which is used for the treatment of excessive day time sleepiness. This can interact with the sodium oxylate, and increases the respiratory and CNS depressant effect of sodium oxylate. Possible reactions are hypotension, profound sedation, and respiratory depression.

Gabapentin

No major interactions have been noticed when pregabalin and gabapentin are co-administered. The pharmacokinetics of gabapentin was found to be unaltered by pregabalin following the single and multiple doses.

So, most of the interactions occur due to the co-administration of pregabalin with other CNS depressants like benzodiazepine, and this thing should always be taken into consideration while taking this drug. Misuse of this drug must be avoided and in especially the elder people suffering from diabetic neuropathy.[20]

CONCLUSION

Pregabalin which is an anti-epileptic drug is used for the treatment of diabetic peripheral neuropathy. Pregabalin is free from protein binding and there is very less amount of metabolism of this drug. Due to these factors, pregabalin shows the very lesser degree of adverse drug reactions and drug interactions. Its use has increased gradually from past few years, though alternative methods are still used to relieve pain. Several clinical and preclinical studies are non-scant from which it can be deduced that how effective the drug is. Pregabalin has made its way to be considered as first line drug for neuropathy besides other drugs like the tricyclic anti-depressant. The main target of this drug is α2-δ Type 1 subunit of voltage gated calcium channel in a pre-synaptic neuron. The drug benefits definitely outweighed the risk associated. The adverse drug reactions are generally not serious though this does not mean it is devoid of serious adverse drug reaction. The only problem with the drug is its dosing, the dose optimum in most of the patients has been found to be between 300 to 600mg/day for 2 to 4 weeks; without this, it cannot be concretely said that the drug would show the desired benefits.

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