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PREGABALIN – A WIDE-RANGING MEDICATION

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Introduction

Pregabalin was used initially as an anxiolytic in the 1990's and trials were conducted in panic disorder, amongst others. Since then, it was introduced in South Africa as a drug for neuropathic pain, registered only for use in diabetic neuropathy and post-herpetic neuralgia.

KEY MESSAGES

- Understanding pregabalin's mechanism of action, supporting the wider use of this agent in specific pain and anxiety conditions
- Chronic pain management in difficult-to-treat patients is guided by attaining 3 initial goals – exogenous opiate removal, reduction in nervous system excitability and restoration of 'normal' sleep patterns
- Other specific conditions that will benefit from pregabalin use are described in a practice-orientated manner, including generalised anxiety disorder, functional pain associated with irritable-bowel syndrom, tension-type headaches and mechanical back pain
- Optimal approaches to the introduction and dosing of pregabalin are described, based on clinical experience, so as to limit side-effects and treatment discontinuation

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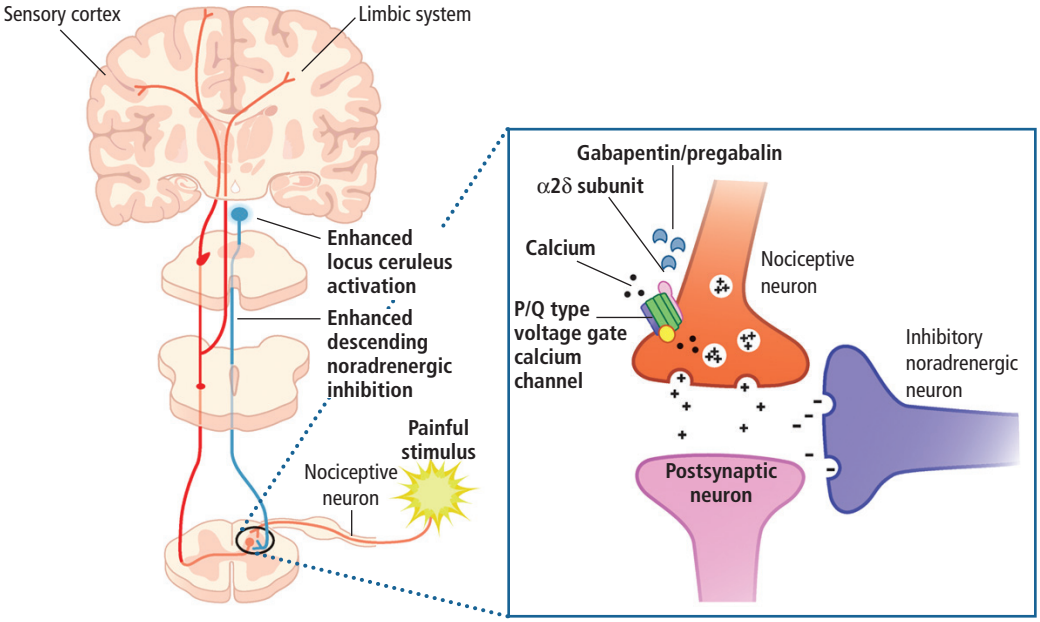

Figure 1. Mechanism of action[1]

Mechanism of action

"Pregabalin has a wide-ranging utility in areas of pain, anxiety and neuromodulation."

The mechanism of action and potential utility of pregabalin is widespread and the off-label uses currently far outnumber the registered ones. Other countries have registered it for use in anxiety disorders and in the EU it is one of the most prescribed drugs for anxiety, providing a safe alternative for the benzodiazepines and the attendant problems with this class. It has also been shown to be a safe anti-epileptic and effective in a wide range of chronic pain conditions especially those that fall into the functional pain category. To understand this use, one has to understand the mechanism of action of this drug, which is not dissimilar to gabapentin in action (Figure 1).

These drugs work via the Ca^{2+} channels which are involved in transmission of nerve signal via an effect on polarity. This then has an effect on the excitability of the nerve and, as a result, the eventual conduction of the signal. This effect is a widespread one, acting in the peripheral nervous system (PNS), the spinal cord and even in the brain tissue. The mechanism of action is thought to occur via attaching to the alpha-2 delta subunit of the voltage gated Ca^{2+} channels in the presynaptic neurone, thereby inhibiting the release of dopamine, norepinephrine, serotonin, substance P and glutamate. It has no effect on gamma-aminobutyric acid (GABA) receptors or metabolism.

The effect of pregabalin is similar to gabapentin but six times more powerful at the receptor site. Logically therefore it would make sense that pregabalin has a wide ranging utility in areas of pain, anxiety and neuromodulation. Multiple studies have been carried out to ascertain the effect of administering pregabalin in peri-operative settings and the consensus is that, if administered pre-operatively, it has great benefit in reducing post-operative pain and the need for opiates and nonsteroidal anti-inflammatory drugs (NSAIDs).[2] Similarly, many trials of pregabalin in anxious patients have indicated its effects vs. placebo are comparable to benzodiazepines. The obvious advantage of pregabalin is the relative lack of tolerance and dependence which the benzodiazepines produce. In Europe, pregabalin is the most prescribed drug for anxiety and preferred to the benzodiazepines for the same reasons.

Chronic pain management

In my experience, running a chronic pain clinic in Durban, KZN; pregabalin has become the cornerstone of management of those difficult patients whom all other specialists have written off. The typical type of patients referred to us as pain

specialists are those who have been living with pain for years and whose entire ecosystem has evolved to adapt to the pain. Their origins may differ but their paths all merge at the point of mood, anxiety and poor quality of life and productivity. The effect is, of course, more far-reaching than their personal domains – families, marriages, friends etc. are all affected in some way. In order to understand this link, one has to understand the context in which the pain presents. These are patients who are generally dependant on or very tolerant to the effects of opiates, having run the gauntlet of almost all of their variants. Then they have the added complication of being clinically anxious and depressed both as a co-morbidity of the pain as well as the effect of long term opiate use. They also are victims of the opioid rebound syndrome where the exogenous opiates suppress the endogenous (endorphin) production, thereby reducing the pain threshold and making them susceptible to hyperalgesia and allodynia.

Physiology of chronic pain

Physiologically, the nervous system is chronically hyperactive from the PNS to the spinal tracts to the thalamus and the cortical structures. The manifestation of this hyperactivity is the physical and psychological symptoms of pain and agitation. It stands to reason that the GABA-glutamate balance is disrupted, as the excitability clearly is in the ascent and the inhibitory influence is overwhelmed. This then represents an abnormal chemical milieu into which the clinician attempts to introduce traditional pain medications like NSAIDs, opiates and paracetamol. This approach does not work. The fundamental principal therefore has to be the attempt to return this abnormal chemical state to one resembling a normal balance before pain control can be achieved.

"The reduction of afferent signals from the periphery and reduction in pain perception is an integral part of managing the chronic pain phenomenon."

Clinical approach to chronic severe pain

Fundamental goals that need to be achieved in the management of chronic severe pain are three-fold (Box 1). By removing all exogenous opiates, the endogenous system can reset itself. Reducing conduction at all levels of the nervous system (peripheral, spinal and cortical) reduces the state of excitability. In a recent review article on the state of nociception and pain research, Baliki and Apkarian (2015) pointed out that the reduction of afferent signals from the periphery and reduction in pain perception is an integral part of managing the chronic pain phenomenon. They also stressed that the onset of chronic pain syndromes and transition from acute to chronic pain is largely a central issue associated with anxiety, mood and other pre-existing predispositions.[3] Sleep is an integral part of pain management as an increase in the amount of slow wave sleep has been shown to have the best effect on pain control. Ensuring good sleep and return to as-normal-as-possible circadian rhythm enables the brain to do all its healing during sleep, cleaning up the "debris" from the previous day.

Box 1. Fundamental goals of chronic severe pain management

1. Remove all exogenous opiates
2. Reduce state of excitability
3. Ensure good sleep and return of circadian rhythm to as close to normal as possible

The role of pregabalin in this approach is three-fold: it reduces nerve conduction in the PNS and central nervous system (CNS), it has an anxiolytic effect and it has an effect on sleep architecture increasing slow wave sleep. In the absence of opiates and combined with a serotonin-norepinephrine reuptake inhibitor (SNRI) such as duloxetine and a safe non-addictive sedative hypnotic, the nett effect is significant. Duloxetine also improves anxiety and mood and reduces pain impulses from entering the thalamus by a spinal inhibition action.

Other areas of clinical utility for pregabalin

Pre-operative pain management in chronic pain patients

Pregabalin is used pre-operatively in chronic pain patients who are most likely going to have more than expected levels of post-operative pain. Once again, patients who have a history of chronic pain syndromes or have been in pain for a significant amount of time as a result of the pathology, should be regarded as high risk to have ongoing chronic pain post-operatively; especially with a history of opiate use for a prolonged period. These patients would benefit from the initiation of pregabalin prior to surgery and continuation post-operatively as an alternative to the opiates.

Detoxification of benzodiazepine addiction

Because of it's benzodiazepine-like effect, pregabalin is used for detoxification from benzodiazepine withdrawals and prevention of relapses. It has also shown to be anti-epileptic in nature, so it's utility in preventing seizures in withdrawal states is helpful. The abuse of benzodiazepines is a worldwide phenomenon and to get patients off this group of drugs, we have had to use other benzodiazepines with longer half-lives in the past (diazepam). Traditional teaching has recommended fairly long-term use of the replacement benzodiazepine (+/-3 months) and now, with pregabalin, this can be avoided as coming off the pregabalin is not as problematic.

Benzodiazepine-contraindicated anxiety disorders

The basis of treatment in anxiety disorders is still primarily the selective serotonin reuptake inhibitors (SSRIs). There are patients that respond well to SSRIs and don't need much else. However, the very nature of anxiety sometimes makes the period of initiating SSRIs difficult, as these patients are more unlikely to tolerate the side effects and the adjustment period. This is often when clinicians use benzodiazepines for a short period, usually two weeks, until the SSRI kicks in. Longer use of the benzodiazepine is discouraged due the risk of the patient becoming abnormally dependant on the immediacy of the effect. Traditionally, there have not been great alternatives to this group of drugs. Pregabalin has utility in generalised anxiety disorder (GAD) where traditional approaches are not sufficient and the use of a benzodiazepine is contraindicated. With the registration of pregabalin for use in anxiety disorders in Europe, it has grown in stature for this very large group of patients. The advantages cited in the clinical trials have been the rapid onset of action, improvement of physical symptoms associated with anxiety and the tolerability of the drug.[4,5] Pregabalin is used not only as an adjunctive treatment, but also as monotherapy in GAD.

Phantom limb syndrome

The literature on pregabalin efficacy for phantom limb syndrome in amputees is equivocal, but there is anecdotal evidence that shows some utility: *"In my pain practice, many patients with phantom pain have responded well to pregabalin."* Having said that, there is also a subgroup of amputees or paralysed patients who have not benefited from the drug. In the final analysis it is an agent worth a try in this population.[6]

The addition of a serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant is recommended, duloxetine preferably, as there is a synergism between these two drugs. One has to bear in mind that the pain may well be related causally and co-morbidly with clinical depression and often post-traumatic stress disorder (PTSD), so the antidepressant serves many roles.

Functional pain syndrome

Functional pain syndromes such as irritable bowel syndrome (IBS), chronic pelvic congestion, tension-type headache (TTH) and mechanical back pain are all generally associated with muscular tone but have a significant neuropathic element. Once again the general view is that these patients have a high neural tone both centrally and peripherally and are traditionally very resistant to most forms of treatment. These patients also end up becoming opiate dependant as a result of being non-responsive to other treatments.

Pregabalin provides a treatment that will address the pain and the anxiety that most of these patients have. It must be remembered that most of these functional pain syndromes are related to a central pathology around pain sensitivity and, after a period of time, peripheral hyperactivity then leads to increased spinal activity. The utility of pregabalin lies in its ability to reduce nerve conductivity in the periphery and spinal column as well as its effect in the brain via the GABA system.

Fibromyalgia

Fibromyalgia pain syndrome (FPS) most classically demonstrates the effect of pregabalin in the CNS and PNS. The combination of duloxetine and pregabalin is considered first-line treatment worldwide for this condition (even though we don't have registration in South Africa). This therapy, the correction of sleep patterns and introduction of appropriate exercise regimens are the best approach to this ubiquitous condition.

Doctors are still mistakenly prescribing long-term opiates to these patients thereby perpetuating the pain and delaying recovery. These patients have a high incidence of mood and anxiety disorders and the origin is becoming more accepted as central in nature. At the pain clinic we combine physical therapies, psychotherapies and medications in order to get the best relief. It must be noted that many patients who present like with fibromyalgia-like symptoms may well have somatoform disorders and making this distinction saves a lot of unnecessary medicating.

Optimal dosing with Pregabalin

The utility of this compound has been in no doubt, especially in the fields of pain management and anxiety. The risks associated with its use are related to dosing and specific vulnerabilities. Pregabalin action has been shown to be optimum at 150mg BD but there is significant utility at 75mg BD and a role for the 25mg dose as well. It has been demonstrated that a slow introduction at lower doses and a gradual build up of the dose, monitoring effect along the way, is best to avoid initial side effects of sedation and motor instability.

"I often start at 25mg *nocte* and increase to BD and slowly get up to 75mg BD where there is often a significant response for pain management. From 75 to 150mg is an easier transition after a few weeks, as the patients get accustomed to the effect of the drug. It also depends on whether there is co-administration with any other sedating agents so be sure to look out for opiates or benzodiazepines, the latter of which can have a cumulative sedative effect in the patient.

Discontinuation of treatment

The main reasons patients discontinue treatment is sedation and imbalance. Over prolonged periods, pregabalin has also been shown to cause weight gain and patients have to be counselled on lifestyle changes specifically around diet and exercise in order to avoid this becoming significant. Pedal oedema, dry mouth, blurred vision and urinary hesitancy have also been described, but these are less reported.

Conclusion

Pregabalin has changed the landscape of pain management in the last few years, specifically chronic pain, but also acute pain and prevention of post-operative pain. It also has other uses by virtue of its mechanism of action, which currently are mostly off-label in South Africa, and one has to keep this in mind when confronted with patients where traditional agents have failed. Using pregabalin appropriately with a knowledge of the effects and side effects will help get patients through the initiation period.

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