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Gabapentinoids in Preventive Analgesia: Pharmacological and Clinical Aspects

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Abstract

Optimal postoperative pain management presents a challenge for healthcare providers across all surgical specialties, since it is estimated that many patients submitted to major surgeries do not receive an adequate analgesic treatment, increasing the risk of complications, length-of-stay and costs for health assistance. The development of new agents for postoperative pain control creates possibilities for better combinations in preventive and multimodal analgesia. Recently, the use of gabapentinoids (gabapentin and pregabalin) in the perioperative period has become more popular. Several clinical studies and meta-analyses reveal that perioperative gabapentinoids may evoke a significant opioid-sparing effect and probably decrease the postoperative pain score. Gabapentinoids may be a good strategy for preventive and multimodal analgesia in major surgeries, particularly pregabalin, considering its pharmacokinetics profile. Situations where there are limitations of regional anesthesia techniques or in cases where there is an intention to reduce the use of opioids or anti-inflammatory drugs at the trans-operative period are certainly good opportunities for their use. However, gabapentinoids are associated with several adverse effects, including sedation, dizziness, and peripheral edema. Therefore, further studies are needed to evaluate the real cost-effectiveness of this approach. Additionally, specific attention should be paid to minor and ambulatory surgeries as well as for the elderly patients to which gabapentinoids are clearly not beneficial and potentially harmful.

Keywords: Gabapentinoids, Preventive analgesia, Pain, Anesthesia, Gabapentin, Pregabalin

1. Introduction

Pain is one of the most common and significant postoperative events experienced by many surgical patients. Optimal postoperative pain management presents a challenge for healthcare providers across all surgical specialties.

Immediate postsurgical pain affects four out of five patients [1]. In a national US survey of adults who had undergone surgery within the previous 5 years, 86% of overall patients experienced postsurgical pain, and 75% of those who reported pain described its severity as moderate–extreme during the immediate postoperative period [2].

The implications of poorly controlled postoperative pain are substantial, including cardiopulmonary complications, opioid-related side effects, unplanned hospital admissions, prolonged hospital stay, increase in health services costs and the subsequent development of chronic pain or opioid addiction [3]. Additionally, it is noteworthy that when surgeons prescribe more doses of opioids or potent opioids when other non-opioid analgesics may be able to control postoperative pain, they are contributing to the opioid epidemic [4].

Recent evidence has raised the importance of preventive analgesia [5, 6] which may be defined as the occasion where the pharmacological intervention is initiated earlier than the painful stimulus to inhibit nociceptive input before it is triggered. It has been demonstrated that preventive multimodal pain therapy has been successfully implemented for numerous surgical procedures, often resulting in decreased opioid consumption and a shorter hospital stay [7, 8]. Medications to achieve opioid-sparing preventive analgesia include non-steroid anti-inflammatory drugs, magnesium, lidocaine, N-Methyl-D-Aspartate (NMDA) receptor antagonists, glucocorticoids, and alpha2-agonists and some anticonvulsant drugs [9].

Moreover, the prescription of the gabapentinoids (gabapentin and pregabalin) in the perioperative period has become increasingly common and they have become ubiquitous components of protocols for early recovery after surgery and preventive and multimodal analgesia.

Despite the existence of several studies comparing the use of these drugs as preoperative medication for the most diverse surgeries, there are conflicting results and no consensus on what the better choice and ideal dose could be [10]. It is generally accepted that the gabapentinoids are effective in reducing immediate postoperative pain and opioid consumption. However, it is noteworthy that the patients' safety has emerged as a broader gabapentinoids concern once these drugs have significant adverse effects as well.

Further definition of uncommon side effects, the optimal preoperative and postoperative doses, treatment duration, and dosage schedule are needed before perioperative gabapentinoids can be broadly recommended as the standard of care for all patients.

Therefore, this book chapter will present a systematic review of literature regarding the pharmacological and relevant clinical features about gabapentinoids for preventive analgesia, including the used drugs with their respective doses, routes of administration, tolerability, and safety profile as well as procedure-related complications and patients' satisfaction.

2. Pain control

The International Association for the Study of Pain (IASP) has stated in 1979 that pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components [11, 12]. Therefore, it is known that the painful experience involves the interpretation of the biological aspects of pain, but also its interaction with the social and cultural characteristics of everyone [13].

Pain plays an important role in biological signaling as a necessary condition for our survival, evoking autonomic, pathological, and psychological responses to prevent tissue damage and it can be classified as acute or chronic pain [14].

The acute condition has a burden beginning, limited duration and it is associated with a local well-established and self-limited cause, with a time course usually lower than 3 months. On the other hand, the chronic pain may be considered a disease state, since it may be understood as the pain that outlasts the normal time of healing (higher than 3 months) and it may arise from psychological states, it serves no biological purpose, and has no recognizable endpoint [15].

Considering its pathophysiology, pain may be classified as nociceptive, neuropathic, or mixed pain. The neuropathic pain is associated with damage to the somatosensory nervous system. On the other hand, the most common is the nociceptive or inflammatory pain which comes from any tissue other than the neurological one. It happens after different types of stimuli, such as physical, mechanical, chemical, infectious and others, which promotes pain and regeneration of the injured tissue. The post-operative pain as well as those related to trauma and ischemic conditions are known as nociceptive pain [16].

The human body has a physiological protection system that acts as a neural network for the perception of harmful stimuli [17]. Briefly, pain processing starts with the information transduction that occurs when peripheral nociceptors are activated and detect a damage or harmful stimulation from the environment, transforming it into an action potential to inform the central nervous system (CNS) of homeostasis alteration. After that, information transmission by free and specialized nerve endings (known as A-delta and C fibers) occurs and the stimulus is carried out to the CNS through afferent pathways crossing the spinal medulla, arriving at the cerebral cortex where pain perception occurs.

Fortunately, the human body has a descending inhibitory system for acting on pain modulation. Central structures located at the brain, hypothalamus, brainstem, and dorsal horn of the spinal cord release mediators such as serotonin, norepinephrine, gamma aminobutyric acid (GABA) and acetylcholine to inhibit the algic stimuli [14].

Pain is a classic problem related to major surgeries, and its inadequate control occurs in a significant number of patients predisposing dissatisfaction and failure to ambulate, resulting in a longer hospitalization, with higher risk of morbidity and mortality [18]. Therefore, the knowledge of pain physiology is essential to understand the mood of action of many medications used in anaesthesiology, including preventive and multimodal analgesia.

3. Gabapentinoids

Gabapentinoids, a class of drugs including gabapentin and pregabalin, were originally marketed in the 1990s for use as antiepileptics but they have anxiolytic effects and subsequently they were approved to treat neuropathic pain conditions [19, 20]. In Anaesthesiology, these drugs have received increased attention in recent years particularly for preventive analgesia while, on the other hand, the prescription of opioids tended to decrease once they were related to adverse events and suboptimal patient outcomes.

Gabapentinoids were designed as GABA analogues although they do not have any effect on GABA receptors directly [21]. These drugs bind to voltage-gated calcium channels, reducing calcium influx inside the presynaptic terminals [21].

The voltage-gated calcium channels are composed of multiple subunits, but the α -2- δ component has a great association with pain processing. Some studies suggest that increased levels of these subunits may lead to neuropathic pain, even without nerve damage [22]. When the nociceptors are sensitized and activated by a minimal stimulation, the action potential transmitted to the dorsal horn allows the activation

of voltage-gated calcium channels and a calcium influx and glutamate release, evoking primary hyperalgesia. In other words, at the site of inflammation and in the dorsal horn, an excitatory signal is produced, increasing postsynaptic nociceptive activation [6, 22]. On the other hand, gabapentinoids can soften the release of excitatory neurotransmitters and reduce the hyperexcitability of dorsal horn neurons induced by tissue injury, explaining their effectiveness on neuropathic pain [22].

Other sites of action involved in the gabapentinoids' analgesic effect have been described with limited evidence, such as sodium channels, NMDA receptors and others. Briefly, a more accurate description of their mechanism is the depression of presynaptic excitatory input onto dorsal horn neurons through interactions with α -2- δ subunit of the voltage-gated calcium channels that are upregulated after injury. Moreover, they inhibit forward trafficking from the dorsal root ganglion, their recycling from endosomal compartments and stimulate glutamate uptake. Additional mechanisms not directly related to neurotransmitter release at dorsal horn include inhibition of descending serotonergic facilitation, stimulation of descending inhibition, anti-inflammatory actions and influence on the affective component of pain [23]. Indeed, a meta-analysis concluded that gabapentinoids can reduce pain scores in the first 24 hours as well as they may decrease the cumulative consumption of morphine and side-effects, such as nausea, vomiting and itching after spinal surgery [24].

In pharmacological aspects, gabapentinoids have only oral presentations and are easily tolerable by the patients. The most common side effects reported are sedation, dizziness or headache, peripheral edema, and visual disturbances [25].

Although gabapentin and pregabalin have similar structure and mood of action, pregabalin presents higher affinity to the calcium channels subunit site which may evoke not just an increased efficacy but also a risk for side effects in situations that require higher doses [23].

The main differences between these two drugs arise not from different modes of action but rather from different bioavailability. Although both drugs are absorbed by amino acid carriers, gabapentin absorption is limited to a relatively small part of the duodenum, whereas pregabalin is absorbed throughout the small intestine [26]. Therefore, gabapentin presents a plasmatic peak concentration in three hours, in opposition with pregabalin which is rapidly absorbed and demonstrates a peak of plasmatic levels in just one hour associated with a more linear pharmacokinetic profile and less variable bioavailability [21].

Gabapentinoids have a low rate of binding with plasma proteins, their metabolism is not dependent on the liver, and they are excreted unchanged in the urine. Also, the elimination half-life ranges of gabapentin and pregabalin are 4.8–8.7 h and 5.5–6.3 h, respectively [22]. On these terms, patients with kidney failure must have a medication dose adjustment [27, 28]. Similarly, these agents should be used with caution, or the dose should be decreased in elderly [29].

4. Gabapentin

Gabapentin was first approved by the Food and Drug Administration in 1993 and it was initially meant to treat seizures, but as time goes by, it started to be used for chronic pain [30]. Gabapentin consists of a GABA molecule covalently bound to a lipophilic cyclohexane ring. Considering its lipophilic profile, it can cross the blood–brain barrier and it can become an active GABA agonist. As an anticonvulsant drug, it can inhibit tonic hindlimb extension in the electroshock seizure model, as well as clonic seizures [30].

Although gabapentin is approved to treat chronic pain with regular doses ranging from 900 to 1200 mg per day, it is also used as antiepileptic medication (900 to

1800 mg daily) usually requiring a second anticonvulsant drug. However, it is not approved by the FDA for treating or preventing surgical pain, despite its off-label use increase worldwide as well as its recommendation for larger doses and longer treatment duration [31–33].

Gabapentin began to be used as a co-analgesic in the preoperative, as the studies showed no risk of intake, besides the fact that it substantially reduces pain during movement and decreases morphine consumption, making it a very promising medication in the opioid sparing or multimodal strategy. Even though the FDA has not approved it for this use, preoperative gabapentinoids have been widely used. The most common side effects associated with gabapentin use were: sedation, dizziness and peripheral edema [34].

Several clinical studies and meta-analyses reveal that perioperative gabapentin helps to evoke a markedly opioid-sparing effect and a decrease in postoperative pain score [35, 36]. In contrast, Verret et al. reported no clinically significant analgesic effect for the perioperative use of gabapentinoids and a greater risk of adverse events [20].

The use of 150 to 1200 mg of gabapentin prior to the surgery, and in the day after is the most common strategy for decreasing narcotics consumption in a multimodal strategy [21]. The use may initiate preoperatively, intra-operatively, or postoperatively. Despite little evidence, some studies recommend: Gabapentin 1200 mg 1-2 h before incision, Gabapentin 600 mg three times a day for 5 days and Gabapentin 600 mg for up to 14 days [21].

However, patients may show some level of sedation and, therefore, it is recommended to avoid its use in ambulatory patients as well as caution use in elderly and in patients with cognitive impairment. On the other hand, there are almost no studies using gabapentin and regional anesthesia, so more data should be gathered in order to develop a safe protocol for larger and more routine use, considering risk and benefits.

5. Pregabalin

The pregabalin is an antiepileptic drug whose effectiveness to treat neuropathic pain was discovered in 1965 [37]. It was originally used in the 1990s as an anticonvulsant drug [20] and in 2004 it was approved by FDA for neuropathic pain, then fibromyalgia in 2007 and spinal cord injury neuropathic pain in 2012 [30]. Over the last decade, pregabalin has acquired a new use, for preventing postoperative acute pain and as an opioid spare strategy, and its use became widespread and routine in some countries [20].

Pregabalin has no activity at GABA receptors, but it acts on binding to the α -2 δ subunit of voltage-gated P/Q-type calcium channels [21]. The α -2 δ receptor has 4 isoforms. The α -2 δ -1 isoform mediates the effects of gabapentinoids, and it is found in the brain, skeletal, cardiac, and smooth muscle. The α -2 δ -2 and α -2 δ -3 isoforms are present in non-neuronal tissues as well, and the α -2 δ -4 subunit is expressed in retinal neurons and other non-neuronal tissues [23].

The binding to the α -2 δ may inhibit or modulate the process of calcium influx through these channels, on the synaptic bulb of presynaptic neurons, thus inhibiting the release of glutamate and substance P. Additionally, the analgesic effect may occur due to activation on the descending inhibitory noradrenergic pathways [21, 37] and due to inhibition of ascending pain transmission [21, 30].

The bioavailability of pregabalin is approximately 90% and its half-life is about 6–7 hours which allows its use twice a day. Its binding to proteins is minimal and the drug is renally excreted [21, 38].

In comparison to gabapentin, pregabalin has an affinity for the type N voltage dependent calcium-channel six times higher [38]. Because of the expression of α -2 δ in cerebellum and hippocampus, pregabalin can cause dizziness, balance disorders, ataxia, visual disturbances, sedation, somnolence, and cognitive impairment [30]. Pregabalin has an antiemetic potential, and it showed significant results for post-operative nausea and vomiting (PONV) reduction, but the primary outcome was never the PONV occurrence [39].

Currently, pregabalin is part of the multimodal anesthetic approach as well as opioid-spare strategy [9, 30]. In addition, although FDA has not approved, pregabalin is used to prevent acute postoperative pain [30].

A 2017 meta-analysis evaluating the use of gabapentinoids for the treatment of acute postoperative pain following spinal surgery showed reduced pain scores compared with placebo. However, the heterogeneity caused by different dosing protocols reduced the level of evidence [24]. In addition, pregabalin seems to be more effective in conditions associated with chronic pain [24]. On the other hand, in an editorial of *Anesthesiology* published in 2020, the evidence of risk of perioperative gabapentinoids was described to increase, while the benefit has diminished [30].

A 2019 review article showed the limited analgesic benefit of gabapentinoids. In addition, they were shown to increase sedation and dizziness. These drugs increase the potential of opioid-induced respiratory depression and sedation, and they are not part of strategy in enhanced recovery [39].

Finally, in a recent meta-analysis it was reported that the perioperative use of gabapentinoids failed to demonstrate differences in postoperative acute, subacute and chronic pain and the adverse effects caused are underreported [20].

Regarding pregabalin use in the context of regional anesthesia, there are few studies published. The use of pregabalin could not reduce the pain scores at rest or with movement with regional anesthesia. The only positive results were the pooled results of both general and regional anesthesia that showed a 24 h opioid consumption reduction. However, there are several limitations of this study, such as heterogeneity and the risk of bias in individual studies [40].

As the use of pregabalin for the management of postoperative pain is *off label*, there are no dosing guidelines for this indication, neither the ideal dose [40] nor the treatment duration are established [21]. Additionally, it is very unlikely that the use of gabapentinoids could provide additional analgesia benefits in the context of regional anesthesia. Only in selected groups there might be some benefits, and these groups are not known. Therefore, this drug, if recommended, should be used cautiously. Further studies are needed to evaluate the real cost-effectiveness of this approach.

The use may initiate preoperatively, intra-operatively, or postoperatively. Despite scarce evidence, some studies recommend: Pregabalin 75–300 mg 1–2 h before incision, Pregabalin 150–300 mg twice a day, with use for 5 days and Pregabalin 150 mg twice a day for 14 days [21].

Patients in hemodialysis demand extra care, because of its renal excretion [39]. Therefore, the maximum daily dose of pregabalin (in mg) and its correlation with creatinine clearance (in ml/min) is: 600 mg if the clearance is higher than 60 ml/min; 300 mg if the clearance range is from 30 to 60 ml/min; 150 mg if the clearance range is from 15 to 30 ml/min; and 75 mg if the creatinine clearance is lower than 15 ml/min [21].

6. Conclusion

Despite the inconsistencies between the reported results, gabapentinoids may be a strategy for preventive and multimodal analgesia in major surgeries, particularly

pregabalin, considering its pharmacokinetics profile. Situations where there are limitations of regional anesthesia techniques or in cases where there is an intention to reduce the use of opioids or anti-inflammatory drugs at the trans-operative period are good opportunities for their use. However, further studies are needed to evaluate the real cost-effectiveness of this approach. Additionally, specific attention should be paid to minor and ambulatory surgeries as well as for the elderly patients to which gabapentinoids are clearly not beneficial and potentially harmful.

Conflict of interest

The authors declare no conflict of interest.

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