CHAPTER **29**

THE USE OF GABAPENTIN AND PREGABALIN AS ADJUNCTIVE POSTOPERATIVE PAIN THERAPIES

Jay D. Ryan, DPM

The use of anti-convulsant pharmaceuticals, particularly alpha-2-delta ($\alpha_2\delta$) calcium channel subunit binders, has become a recent method of early postoperative pain control and represents an innovative analgesic drug class. With many adjunctive pain medications already in use, including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, and cyclooxygenase (COX-2) NSAIDs, the use of a new analgesic class must be justified. Gabapentin and pregabalin, referred to as gabapentinoids, will be reviewed for benefits in postoperative pain, opioid sparing effects, dosing guidelines, and side-effect profile. Also, an assessment of the pharmacologic effects of gabapentinoids and multiple drug trial results will be reviewed in detail.

Gabapentin was developed in the late 1970s and was first utilized in 1993 as an anticonvulsant medication, but was noted to have beneficial effects on neuropathic pain. Treatments later expanded to include diabetic poly-neuropathy, postherpetic neuralgia, fibromyalgia, generalized anxiety disorder, and neuropathic pain.[1] Pregabalin was developed over a decade later and has a comparable clinical treatment application. It has benefits over gabapentin with less drug interactions, lower dosing frequency, and dose-independent absorption. Utilizing gabapentinoids, treatment of neuropathic pain was later correlated with postoperative pain control based on early studies linking analgesia after tissue injury to possible postsurgical pain control.[2,3] Due to this research, randomized controlled trials (RCTs) were first conducted in the late 1990s and early 2000s for post-surgical analgesic properties of gabapentin and pregabalin, respectively.

Gabapentinoids have been utilized as treatments for many disorders with only modest evidence behind their mechanism of action. However, recent studies have proven numerous pharmacologic effects including specific amino acid competition for membrane transport, increasing gamma-aminobutyric acid (GABA) concentration in the brain, and activation of ATP-sensitive potassium channels.[4] Newer studies however, suggest strongly that the mechanism responsible for analgesia is due to binding of the $\alpha 2\delta$ subunit of N-type voltage gated calcium channels by gabapentin and pregabalin and is based upon multiple selective-engineering animal studies. Field et al examined single point mutation mice bred for decreased pregabalin binding capability at the above mentioned subunit. After external nerve injury to the mutant mice, gabapentin was administered and the mice exhibited no pain relief response, while placebo mice responded to nerve injury treatment.[5] Additional trials have supported these results and expanded the research to include beneficial effects on both neuropathic and post-traumatic pain. Multiple trials favor binding to the $\alpha_2\delta$ subunit as the most likely and significant aspect of the analgesic mechanism of gabapentin and pregabalin.[4-7]

Acquaintance with the basic pharmacology of these medications is important for use in a post-surgical setting. Gabapentin is maximally absorbed over 2 to 3 hours and has a half-life of 5 to 9 hours. Starting dosages range from 100-900 mg per day and extend to 3600 mg per day maximally. Most commonly, dosages extend between 1200-2400 mg per day given over 8 hour increments. There is 1 reported drug interaction with oral antacids, which reduce the bioavailability by 20-30%, however, no hepatic inhibition or induction is recorded.[8] Pregabalin is maximally absorbed in about 1 hour, with a half-life of 4 to 7 hours. Starting dosage is 75-150 mg per day, and the maximal dose is 600 mg per day. Usually, pregabalin is dosed between 150-600 mg per day. There are no significant drug interactions and no hepatic inhibition or induction as with gabapentin.[9] Both medications need adjustment for renal insufficiency based on creatinine clearance, due to unchanged excretion in the urine. In this case, it is recommended to start with lower doses than recommended above and to slowly titrate up the dose, in order to minimize side effects.

Many RCTs have examined gabapentin and pregabalin for postoperative pain control. These studies differ in the timing and duration of drug introduction, with most trials starting the drug preoperatively, and giving only 1 preoperative dose. Variation exists between trials, with dosages ranging from 300 mg to 1800 mg per day, duration ranging from 1 to 3 days, and surgical procedures performed varying as well. Specific drug trials will be discussed in detail, but it should be noted that due

to the heterogeneity of these trials, cumulative outcomes must be withheld until larger or multi-center trials are performed with similar parameters.

Hurley et al showed that perioperative use of gabapentin decreases pain intensity and opioid consumption in the first 24 hours after surgery. The only side effect recorded was a modest increase in sedation.[10] Ho et al similarly demonstrated that a single preoperative 1200 mg or less dose of gabapentin resulted in less pain and opioid usage, and found a decrease in opioid-related adverse effects such as pruritis and vomiting, for the first 24 hours post-operatively.[11] In addition to these trials, gabapentin has been shown superior to placebo for analgesic effect in over 70% of recent RCTs.[4]

Pregabalin has also been shown to be effective for pain reduction and decreasing opioid usage. Reuben et al have shown this effect in spinal fusion surgery with a pregabalin dose of 150 mg 1 hour preoperatively and 12 hours post-operatively. Pregabalin was administered with celecoxib 200 mg, and then compared with placebo and to both drugs individual effects. Over the first 24 hours postoperatively, pain at rest, pain with movement, and patient-controlled analgesia (PCA) morphine usage was significantly lower in the combination group. A decrease in side effects such as nausea and sedation were also seen in the combination group of pregabalin and celecoxib.[12]

In a study examining delivery of gabapentin, Pandey et al found that in donor nephrectomy patients there was no statistical difference in preincision or postincision delivery, measured by postoperative pain scale and fentanyl consumption. Gabapentin 600 mg was utilized 2 hours preincision or placebo was given, and then the opposite agent was dispensed postincision. A third total placebo group was used for comparison to the gabapentin groups. While decreased pain scales and fentanyl consumption were noted with both gabapentin groups when compared with the placebo group, there was no significant difference in either pre or postincision delivery.[13]

RCTs have shown a range, not only in time of delivery, but also in the dosage of medication dispensed. One such study by Pandey et al used patients undergoing lumbar discectomy to show that with one-time pretreatment of gabapentin, a dosage of 600 mg was the maximal dose at which significant pain reduction was observed. Lower dosages were correlated to less analgesia, and higher dosages showed no significant additional benefit, up to the ceiling trial dose of 1200 mg. At all times in this study, visual analog pain scales and fentanyl analgesic use were significantly decreased when compared with placebo.[14]

The use of gabapentin has also been compared with other adjunctive pain medications. Pandey et al compared postoperative effects of gabapentin and tramadol and found there was a significant decrease in fentanyl consumption and postoperative pain intensity with gabapentin compared with tramadol. This trial utilized a single dose of 300 mg gabapentin, 2 hours before undergoing laparoscopic cholecystectomy.[15]

In an intriguing study, Gilron et al examined the use of gabapentin compared with rofecoxib (COX-2 NSAID) and placebo after abdominal hysterectomy, as well as the effect of gabapentin and rofecoxib in conjunction together. Gabapentin was dosed at 1800 mg per day for 3 days, with PCA morphine available. The combination of medications reduced morphine consumption and pain during the first 24 hours more effectively than either medication independently.[16] Similarly, Durmus et al found that when gabapentin was combined with acetaminophen in abdominal hysterectomy, there was a significant decrease in post-operative pain and opioid use when compared with the use of gabapentin or placebo alone. In this trial, a single 1200 mg dose of gabapentin was used 1 hour prior to surgery. In the first 24 hours, morphine use was decreased by half in the combination group compared with placebo. Additionally, decreased postoperative movement scores were noted in the combination group, but postoperative sedation scores were also increased in both gabapentin groups.[17]

Lower extremity surgical trials include work by Menigaux et al, who supported an anxiolytic effect, in addition to postoperative pain reduction in anterior cruciate ligament repair. With the use of a single 1200 mg dose of gabapentin 1 to 2 hours before surgery, they found improvement in knee flexion angles on postoperative days 1 and 2, a decrease in morphine use by over half, and a decrease in visual analog pain scales both at rest and after movement.[18] Movement-evoked pain is significant in any lower extremity surgery, and it should be noted that 11 of 16 RCTs examining this parameter have shown a significant decrease in movement related pain with use of gabapentin.[4] Gabapentin and pregabalin have been hypothesized to benefit in this instance by preventing central neuronal sensitization.

Turan et al studied scar revision and skin grafting, alone or in combination, on the lower extremity with epidural PCA. Gabapentin 1200 mg or placebo was utilized 1 hour before surgery and also on postoperative day 1 and 2. A significant decrease in verbal pain rating scales were noted for the first 16 hours compared with placebo, and epidural PCA use was decreased through 72 hour monitoring. Despite an increase in dizziness, patient satisfaction was reported to be higher in the gabapentin group.[19]

The side effect profile of gabapentinoids must be examined before surgical worth can be determined. The majority of trials have shown no adverse effects or no significant difference in side effects when compared with

placebo. Among RCTs designed to examine these effects, reports include sedation,[15,16,20] nausea,[15] dizziness,[19,21] vomiting,[21] headache,[22] and blurry vision.[22] It has also been reported that both gabapentin and pregabalin usage has decreased urinary retention,[23] common opioid side effects,[23] headache,[24] vomiting,[23] and sedation.[12] Discrepancies most likely result from the spectrum of surgical procedures, anesthesia, pain medications, and dosage of adjunctive medications. It should be noted that alternative adjunctive medications pose risks for adverse effects, which may be more serious than with gabapentin or pregabalin. Opioid use is limited by nausea, vomiting, sedation, pruritis, and urinary retention. The use of NSAIDs is associated with gastrointestinal mucosal damage, bleeding, renal toxicity, heart failure, and allergic reaction. Additionally, the use of COX-2 NSAIDs may increase thrombotic risk in certain individuals, leading to cerebral vascular accident or myocardial ischemia.[1]

Overall literature support has been favorable for the use of these medications. A review of all available RCTs concluded an opioid sparing effect of 20-62% in the first 24 hours, with single preoperative dosing of gabapentin 300-1200 mg given 1 to 2 hours before surgery.[1] Gilron found that while 5 of 27 RCTs showed no benefit in opioid sparing or pain score reduction, 21 of 30 double blinded, placebo-controlled, randomized trials confirm post-operative analgesic value.[4] Additionally, an overall reduction was noted in opioid related adverse effects with use of gabapentin, including nausea, vomiting, and urinary retention. The possibility of decreasing movement-related pain following surgical procedures with gabapentin could also be extremely beneficial in lower extremity surgery.[1,18] Broad conclusions on the clinical value of these medications must be withheld due to the heterogeneity of these trials, as well as the limited time-span of research. Larger trials, specific procedure effectiveness, and standardized dosing represent some areas with which further study is needed. However, the short-term dosing, limited side effect risk, and lack of drug interactions make this an easy adjunctive pain control option with effectiveness in both movement-evoked pain and pain at rest, while decreasing opioid usage and possibly side effects related to their use.

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