



Gabapentin Use in Postoperative and Neuropathic Pain in Children

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Gabapentin has become a useful component of multimodal analgesic regimens for many patients. Although initially approved by the Food and Drug Administration in 1993 for the management of partial onset seizures, it is now considered a first-line treatment for the management of neuropathic pain.¹ Gabapentin is also increasingly being used in the postoperative setting to provide analgesia and reduce emergence reactions following anesthesia.^{2,3} While not approved as an analgesic in children, a growing body of literature suggests that it may be a useful adjunct in the pediatric population.

Mechanism of Action

Gabapentin, 1-(aminomethyl)cyclohexaneacetic acid, is a structural analogue of gamma-aminobutyric (GABA). In spite of its name, gabapentin has no activity at (GABA) receptors. It is believed to produce analgesia by binding to the α -2- δ -1 subunit of presynaptic voltage-gated calcium channels in the central nervous system and dorsal horn of the spinal cord. Inactivation of these channels reduces the release of excitatory neurotransmitters, including glutamate and substance P, producing both acute and sustained analgesia. There may be other mechanisms involved, but these have not yet been well defined.¹⁻⁵

Pharmacokinetics

The bioavailability of gabapentin is inversely related to dose, decreasing from 60% with a dose of 900 mg/day to only 27% with a dose of 4800 mg/day. Food has little effect on the rate or extent of absorption.⁴ Peak plasma levels of 2.7-2.99 mg/L are reached in approximately 3-3.5 hrs in adults. Gabapentin is only minimally bound to serum proteins (< 3%) and has a mean volume of distribution of 0.6-0.8 L/kg. It is eliminated by renal excretion as unchanged drug, with an elimination half-life in adults of 5-7 hours and a clearance of approximately 90 mL/min.

In a pharmacokinetic study of 48 children between 1 month and 12 years of age, a single gabapentin dose of 10 mg/kg resulted in peak plasma concentrations at 2-3 hours.⁶ Patients less than 5 years of age had a mean maximum concentration (C_{max}) lower than older children (3.74 ± 1.25 mcg/mL vs 4.52 ± 1.19 mcg/mL, $p < 0.05$) and their area under the concentration-time curve (AUC) was 20% lower than older children (25.6 ± 10.4 mcg•hr/mL vs 36.0 ± 9.37 mcg•hr/mL, $p < 0.001$). When normalized for weight, younger children also had a higher rate of clearance (7.40 ± 2.30 mL/min/kg vs 4.41 ± 0.93 mL/min/kg in older children, $p < 0.001$). Elimination half-life was similar across the ages studied, with an average of 4.44 ± 1.32 hours.

The authors of the study concluded that children less than 5 years of age may require a 30% higher daily dose of gabapentin than older children to achieve similar plasma concentrations.⁶ A second study conducted in 253 children between 1 month and 13 years of age confirmed the higher rate of clearance in children less than 5 years of age, with the greatest variation occurring in infants.⁴

In studies of adults, renal impairment leads to a significant prolongation of gabapentin clearance. In patients with a severe renal impairment (creatinine clearance less than 30 mL/min), the average half-life was 52 hours with a rate of renal clearance of 10 mL/min. Gabapentin doses should be adjusted in patients with renal impairment; no adjustment is necessary for patients with hepatic impairment.

Clinical Experience

Postoperative Pain

The safety and efficacy of gabapentin in children undergoing surgery has been evaluated in several clinical trials. In 2010, Rusy and colleagues conducted a randomized double-blind placebo-controlled trial of gabapentin in 59 children 9 to 18 years of age undergoing spinal fusion.⁷ Patients were randomized to receive gabapentin

15 mg/kg or placebo prior to standardized anesthesia. After surgery, patients received standardized patient-controlled analgesia (PCA) and continued on gabapentin 5 mg/kg or placebo every 8 hours for 5 days. The primary endpoints were opioid consumption, pain scores, and the presence of opioid adverse effects.

Morphine consumption was significantly lower in the gabapentin group in the recovery room (0.044 ± 0.017 mg/kg/hr vs 0.064 ± 0.031 mg/kg/hr in the controls, $p = 0.003$). The differences were also significant on postoperative day 1 (0.046 ± 0.016 vs 0.055 ± 0.017 , $p = 0.051$) and day 2 (0.036 ± 0.016 vs 0.047 ± 0.019 , $p = 0.018$). Pain scores were significantly lower in the gabapentin group while in the recovery room (2.5 ± 2.8 vs 6 ± 2.4 , $p < 0.001$) and the morning after surgery (3.2 ± 2.6 vs 5 ± 2.2 , $p < 0.05$), but were not significantly different between groups during the remainder of the study. There were no differences in the incidence of opioid-related adverse effects.

In 2013, Salman and colleagues studied gabapentin premedication on the frequency of emergence reactions and analgesic requirements following sevoflurane analgesia in children.⁸ A total of 46 children between 3 and 12 years of age undergoing tonsillectomy and adenoidectomy were randomized to receive either gabapentin 15 mg/kg orally 30 minutes prior to induction of anesthesia or a saline placebo. Emergence reactions and anxiety were assessed with a 5-point scale every 10 minutes for 30 minutes. Parents were contacted the day following surgery to provide an evaluation of pain control, analgesic use, parent satisfaction, and the presence of adverse effects.

The frequency of emergence reactions (scores of 4 or 5) was significantly lower in the children given gabapentin than in the controls at both the 20 and 30 minute assessments (47.8% vs 78.2%, $p < 0.01$ and 30.4% vs 56.5%, $p < 0.05$, respectively). Total acetaminophen consumption at 24 hrs was also significantly lower with gabapentin (1.68 doses vs 3.29 doses, $p < 0.01$). There was also a significant difference in parent satisfaction scores, with a median score of 3.70 (range 3-4) in the gabapentin group compared to 2.91 (range 1-4) in the controls, $p < 0.05$. There were no reported adverse effects.

Mayell and colleagues at Toronto's Hospital for Sick Children conducted a similar randomized double-blind placebo-controlled study of gabapentin in children and adolescents (10-17 years of age) undergoing scoliosis surgery.⁹ Thirty-six patients were randomized to receive either gabapentin 600 mg orally or placebo 1 hour before surgery. Anesthesia was infused with fentanyl, propofol, and rocuronium and maintained with remifentanyl and propofol. Postoperative pain management included

morphine PCA and acetaminophen. Postoperative nausea and vomiting was treated with dimenhydrinate or ondansetron. Outcome measures included total morphine consumption within the first 24 hours, time to first dose of rescue analgesia, pain scores, the presence of adverse effects, and patient satisfaction.

While there was slightly less morphine consumption in the gabapentin group at 1 hour, the results were not significantly different (0.087 ± 0.06 mg/kg vs 0.121 ± 0.06 mg/kg in the controls. There was also no difference at 24 hrs (1.29 ± 0.44 mg/kg vs 1.46 ± 0.68 mg/kg). Mean time to rescue analgesia was 25.5 min in the gabapentin patients and 24 min in the controls. One patient in the gabapentin group did not require rescue analgesia. There was no difference in adverse effects. The authors theorized that the lack of benefit may reflect the need for more analgesia after extensive surgeries such as this and suggested that a higher preoperative dose and/or additional postoperative doses may be needed to optimize the benefit of gabapentin.

In 2015, Amani and Abedinzadeh reported the results of their randomized double-blind study comparing gabapentin, bupivacaine, and meperidine for analgesia in children undergoing tonsillectomy.¹⁰ A total of 105 patients (mean age 10.1 ± 3.6 years) were randomized to oral gabapentin (20 mg/kg given 1 hr before surgery), local infiltration of bupivacaine 0.25% (2.5 mL injected into each tonsil bed), or meperidine (1 mg/kg given IV after intubation). All patients received the same anesthesia and acetaminophen every 6 hrs after surgery. Pain was assessed with the Oucher scale at 3 hrs, 6 hrs, 12 hrs, and 24 hrs. The mean pain score was lowest in the gabapentin group at each assessment; the results were statistically significant at 3 hrs, 6 hrs, and 12 hrs. At 3 hours, the mean score in the gabapentin group was 3.5 ± 2.5 , compared to 5.5 ± 3.1 in the bupivacaine group and 4.3 ± 3.5 in the meperidine group ($p = 0.032$). By 6 hours, the values were 2.3 ± 2.1 , 3.9 ± 2.2 , and 3.5 ± 2.5 for the three groups, respectively ($p = 0.012$). At 12 hours, the values were 1.6 ± 1.3 , 3.1 ± 2.5 , and 2.5 ± 1.8 ($p = 0.008$).

Postoperative Nausea and Vomiting

Long-term treatment with gabapentin may also be useful in patients with refractory nausea and vomiting after neurosurgery. Tsai and colleagues found that gabapentin reduced postoperative vomiting in an 11-year-old girl and a 4-year-old boy who underwent craniotomies for posterior fossa tumor resection.¹¹ Both patients continued to experience episodes for 2 months following surgery that did not respond to antiemetics. The 11-year-old patient was treated with a gabapentin dose of 300 mg orally twice daily and the 4-year-old received 100 mg twice daily. Neither patient experienced adverse effects.

Neuropathic Pain

Gabapentin has been used in the management of pediatric neuropathic pain for nearly two decades. In 1998, McGraw and Stacey described the effective use of gabapentin in a 12-year-old girl with neuropathic pain after thoracotomy for a pacemaker revision.¹² She described her pain as knife-like and almost constant. Trials of diazepam, oxycodone, and nonsteroidal anti-inflammatory drugs (NSAIDs) failed to resolve her pain. She experienced slight improvement with amitriptyline and oral methadone. An infusion of lidocaine produced relief but caused disorientation requiring discontinuation. Gabapentin was then initiated and titrated over the next 3 weeks to a dose of 300 mg three times daily. At this dose, she reported nearly complete resolution of her pain. There were no adverse effects noted. Gabapentin was weaned off after 4 months without recurrence of her pain.

Two years later, Wheeler and colleagues reported success with gabapentin in a 9-year-old girl with reflex sympathetic dystrophy (RSD) in her left lower extremity.¹³ Based on previous reports describing successful treatment of RSD in adults, gabapentin was initiated at a dose of 100 mg once daily. The patient had significant improvement within days. Her dose was increased to 100 mg twice daily several weeks later, after a return of her pain and allodynia, with resolution of her symptoms.

In 2007, Low and coworkers conducted a retrospective study of 20 children with complex regional pain syndrome (CRPS) at the Children's Hospital at Westmead, Sydney.¹⁴ Ninety percent of the patients were female, with a mean age of 11.8 years (range 8-16 years). The lower limbs were the most common area affected, and in 80% of patients, CRPS was initiated by minor trauma. In addition to acetaminophen, NSAIDs, or opioids, 13 patients (65%) received amitriptyline (10-20 mg prior to bedtime) and three were treated with gabapentin (300 mg at bedtime, titrated to 300 mg three times daily as needed). Both agents were effective. There were no reported adverse effects. The authors noted that these agents were typically initiated early in the course of treatment to facilitate physiotherapy. Mean time from diagnosis to symptom resolution was 11 weeks (range 3 days to 26 weeks).

Akkurt and colleagues recently described an additional case of gabapentin use in a child with sciatic nerve injury.¹⁵ The 12-year-old boy had developed severe neuropathic pain after sciatic damage from a gunshot wound 2 months earlier. Rehabilitation had been delayed due to allodynia resulting in inability to tolerate stretching or other therapies. Gabapentin was started at a dose of 10 mg/kg/day and later titrated to 16 mg/kg/day. Within the first week, the patient's pain declined and the rehabilitation program was able to begin. Within the second week, the

patient rated his pain as a 3 on the visual analog scale, significantly improved over his previous scores of 10. His score on the scale for assessment of neuropathic symptoms and signs (LANSS) decreased from a baseline of 22 to 0. The patient reported dizziness the first 1-2 days, but no other adverse effects. With the patient's continued improvement, gabapentin was able to be weaned off after 2 months of therapy.

Gabapentin has also been used in the treatment of neuropathic pain in infants.^{16,17} A recent case series described 11 infants with pain associated with complex neurologic, pulmonary, or gastrointestinal disease. There were eight premature infants (median gestational age 25 weeks) and three term infants. The average age at the start of treatment was 143 days in the premature infants (range 98-253 days) and 131 days in the term infants (range 48-182 days). Gabapentin was initiated at a dose of 5 mg/kg every 8, 12, or 24 hrs. Six patients had decreased irritability after initiation of treatment; another two had improved feeding tolerance. Five patients were able to wean off opioid and benzodiazepines. Adverse effects included bradycardia in three patients and rebound tachycardia with abrupt discontinuation of gabapentin in two patients which resolved with restarting at a lower dose.

Warnings and Precautions

Gabapentin has been linked to hypersensitivity reactions, including anaphylaxis and angioedema.⁴ These reactions have been reported with the first dose, but may occur at any time during therapy. Drug reaction with eosinophilia and systemic symptoms (DRESS) has also been reported in patients receiving gabapentin. These reactions can progress to multiorgan system failure and death. Gabapentin should be discontinued in patients who develop a rash, fever, or lymphadenopathy and only resumed when a potential drug-associated hypersensitivity reaction has been ruled out.

As with all antiepileptic drugs, gabapentin may increase the risk for suicidal thought or behavior. Patients who will be receiving long-term therapy and their families should be aware of this risk and the need to report any change in behavior or mood to a healthcare provider.

Adverse Effects

In pooled data from placebo-controlled clinical trials of gabapentin in children and adolescents with seizures, the most commonly reported adverse effects included fever (in 10%), nausea and vomiting (10%), somnolence (8%), hostility or emotional lability (4-8%), and dizziness or hyperkinesia (3%).⁴ Gabapentin has been well tolerated in surgical patients. There is currently not enough data with the use of gabapentin in pediatric neuropathic pain to define the adverse effect profile associated with that use.

Drug Interactions

Concurrent use of gabapentin and morphine may result in additive somnolence and central nervous system or respiratory depression.⁴ Mean gabapentin AUC values increased by 44% in adults given morphine while taking gabapentin. Administration of gabapentin with hydrocodone decreases hydrocodone AUC in a dose-dependent manner, from a 3-4% reduction after a 125 mg dose of gabapentin to a 21-22% reduction with a 500 mg dose. Concurrent use of naproxen sodium may reduce gabapentin absorption by 12-15%. Administration of aluminum hydroxide and magnesium hydroxide antacids has been shown to reduce the bioavailability of gabapentin by 20%. Gabapentin should be taken at least 2 hours after an antacid.⁴

Availability and Dosing Recommendations

Gabapentin is available as the brand name product (Neurontin[®]) or as generic products in 100 mg, 300 mg, 400 mg capsules, 600 mg and 800 mg scored tablets, and a 50 mg/mL oral solution. The solution must be kept refrigerated.⁴ Gabapentin may be taken with or without food.

In children and adolescents undergoing surgical procedures, a single gabapentin dose of 10-15 mg/kg oral dose (maximum 600 mg) may be administered prior to induction of anesthesia. Gabapentin may be continued after surgery at a dose of 5-15 mg/kg/day divided and given every 8 hours in children 3-12 years of age.¹ In patients more than 12 years of age, the recommended starting dose is 300 mg every 8 hours. The dose may be increased to 600 mg every 8 hours if needed.

In adults or adolescents weighing 50 kg or more who are being treated for neuropathic pain, dosing should begin with 300 mg once daily (typically at bedtime) with a daily increase in dose frequency to 300 mg every 8 hours by day 3.⁴ The dose may then be further increased as needed to a total of 1800 mg/day. There are currently only limited data to support a dosing recommendation for infants and children; previous reports suggest starting at 10-15 mg/kg/day divided and given every 8 hrs, the same regimen approved for use in children with seizures.⁵⁻¹⁶ Gabapentin doses should be reduced in patients with renal impairment.

Summary

Gabapentin appears to be a useful option for pain management in children. Several studies have documented benefit in the postoperative setting. Several case reports and small retrospective studies also suggest benefit in children with neuropathic pain. Its relatively mild adverse effect profile and lack of significant drug interactions make gabapentin an appealing addition to multimodal analgesic regimens.

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