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Pediatric Use of Gabapentin

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Gabapentin, initially developed as an anticonvulsant, has now found an additional role as an adjunctive therapy for the management of neuropathic pain in children and adults. It is generally well tolerated and offers several advantages over older anticonvulsants, with a milder adverse effect profile and few drug interactions.[1-3] This article will review the use of gabapentin in children, both as an anticonvulsant and as an analgesic.

Mechanism of Action

The mechanism for the anticonvulsant and analgesic actions of gabapentin is not well understood. Although structurally related to gamma-aminobutyric acid (GABA), gabapentin does not interact with GABA receptors or alter GABA concentrations. A gabapentin binding site has been found in the neocortex and hippocampus of rat brain tissue; however, the functional correlate of binding at this site is not yet known.[2,3] The analgesic effect of gabapentin appears to result from prevention of both allodynia (the pain response to normally innocuous stimuli) and hyperalgesia (an exaggerated response to painful stimuli). In animal models, gabapentin has been found to be effective in preventing responses to neuropathic pain and the pain associated with peripheral inflammation. Gabapentin does not appear to alter response to immediate pain.[3]

Indications

Gabapentin is currently approved by the Food and Drug Administration (FDA) as adjunctive therapy in the treatment of partial seizures in adults and children over 3 years of age. It is also indicated for the management of postherpetic neuralgia in adults.[2,3]

Use as an Anticonvulsant

There are several studies of gabapentin in children with partial seizures. In 1996, Khurana and colleagues reported the results of an open-label add-on trial in 32 children (ages 2-16 years) with refractory partial seizures.[4] The children were treated with gabapentin doses of 10 to 50 mg/kg/day, with an average effective dose of 26.7 mg/kg/day. Eleven children (34%) had a 50% or greater reduction in seizure frequency during treatment. Another 4 children had at least a 25% reduction. Of the seven children who remained in the study at 6 months, two were seizure free, and four had only rare seizures.

Three years later, Appleton and colleagues, publishing as the Gabapentin Pediatric Study Group, reported the results of a 12-week, multicenter, double-blind trial of gabapentin in children with refractory partial seizures.[5] After a 6-week baseline assessment period, 257 children between 3 and 12 years of age were randomized to receive gabapentin (titrated to 25-35 mg/kg/day) or placebo in addition to their standard anticonvulsant regimen. Reduction in seizure frequency, compared to baseline, was significantly better in the gabapentin-treated patients overall (least squares mean –0.161 versus –0.072 in the controls); however, the percentage of patients who achieved at least a 50% reduction in seizure frequency was no different between the groups (21.2% versus 17.5%). Children with complex partial seizures showed the greatest degree of improvement.

A 24-week, multicenter, open-label follow-up trial was also conducted by the Gabapentin Pediatric Study Group.[6] A total of 237 children (3 to 12 years of age) were enrolled in this study. Gabapentin doses ranged from 24 to 70 mg/kg/day. The median reduction in partial seizure frequency was 34% overall. A median reduction of 53% was observed in patients with simple partial seizures, 38% in those with complex partial seizures, and 35% in patients with secondarily generalized tonic-clonic seizures. Concurrent anticonvulsant regimens were unchanged in 185 (78%) of the children at the end of the study. Twenty-seven children (11%) were able to decrease the dosage of their

other anticonvulsants, but the remaining 25 required increased doses of their other therapies.

Similar results were reported by Korn-Merker and colleagues from their prospective, open-label, add-on trial.[7] Fifty-two children and adolescents (1-17 years of age) were given gabapentin at doses of 26 to 78 mg/kg/day, in addition to their usual anticonvulsant regimen, for up to a year. Fifteen of the children (29%) had a reduction in seizure frequency with the addition of gabapentin. Of these, 3 children (6%) became seizure-free. Seizure frequency was unchanged in 65% of the children.

These studies, as well as those conducted in adults, demonstrate the potential role of gabapentin in treating partial seizures. While useful in reducing seizure frequency in approximately a third of patients treated, many patients in these trials did not gain significant benefit from the addition of gabapentin. At this time, gabapentin should be considered as adjunctive therapy for children who continue to have seizures on conventional regimens.

Use as an Analgesic

Many of the traditional anticonvulsants have been found to be useful in the treatment of neuropathic pain, perhaps because of the similarity between the mechanisms of seizure and pain propagation.[8] From shortly after its release onto the market in 1994, gabapentin has been used for the management of neuropathic pain in children and adults.[8-14]

While the mechanism for the analgesic effect of gabapentin remains unknown, the response has been demonstrated in a number of publications. To date, most of the literature in this area has been case reports, with only a small number of clinical trials. In a recent review of 35 papers involving over 700 patients of all ages, Mellegers, Furlan, and Mailis concluded that gabapentin provided a positive benefit in a number of different types of neuropathic pain, including diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, complex regional pain syndromes, headaches, pain following spinal cord injury, and pain associated with multiple sclerosis. They also suggested that prospective studies be conducted to clarify the relationship between symptoms and dose response.[9]

Several pediatric case reports and case series have described the use of gabapentin in children with neuropathic pain.[11-14] In 1998, McGraw and Brett successfully used gabapentin in a 12 year old girl with post-thoracotomy pain of 3 months' duration.[11] Numerous other therapies, including oral opioids, benzodiazepines, and non-steroidal anti-inflammatory agents, were ineffective. At a gabapentin dose of 300 mg three times daily, she had a 90% resolution of pain with no adverse effects. After 4 months of treatment, she was gradually tapered off without recurrence of pain.

Gabapentin has also been used for reflex sympathetic dystrophy, autonomic dysregulation, and phantom limb pain in children.[12-14] Rusy and colleagues reported 7 cases of successful gabapentin use in children and young adults with limb pain following amputation.[13] The patients (ages 4-25 years) were treated with doses of 14-40 mg/kg/day. There was no correlation between age and optimal dose. Time to achieve pain resolution ranged from 1 week to 2 months, and the length of therapy ranged from 1 to 3 years.

In 2001, Behm and Kearns described the treatment of a 3 week old male with amyoplasia congenita resulting in severe contractures and dislocated joints.[15] Because acetaminophen and ibuprofen failed to provide adequate pain relief, gabapentin was initiated at a dose of 7 mg/kg/day (given once daily). Pain scores reached the target range within 72 hours. No adverse effects were noted. The dose was increased to 10 mg/kg/day prior to discharge to further improve patient comfort during handling.

Other Uses

Gabapentin has also been effective in several other types of neurologic and/or behavioral illnesses.[8,16,17] It has been used to reduce anxiety and agitation in patients with bipolar disorder and schizoaffective disorder. Gabapentin has also been reported to reduce self-injury in a 3 year old boy with Lesch-Nyhan syndrome[16] and to reduce extraneous motor movement in a 13 year old girl following a stroke.[17]

Pharmacokinetics

Gabapentin is available only in oral dosage forms. The oral bioavailability of gabapentin is approximately 60%. Food has only a slight effect on absorption, increasing the maximum concentration by approximately 14%. Gabapentin is widely distributed, with less than 3% bound to serum protein. Cerebrospinal concentrations at steady-state are approximately 20% of serum concentrations. Gabapentin is not significantly metabolized. It is eliminated as unchanged drug by renal excretion, with a half-life of 4 to 5 hours in adults. Dosage adjustment is necessary in patients with renal dysfunction.[2]

The population pharmacokinetics of gabapentin in children have been studied in both single and multiple-dose studies.[18,19] In the single-dose

study, 48 children (ages 1 month-12 years) were given a 10 mg/kg oral gabapentin dose.[18] Serum samples were obtained over a 24-hour observation period. Mean area-under-the-serum concentration curve (AUC) values were significantly lower in the younger children (25.6 mcg/ml/hr in patients < 5 years of age versus 36.0 mcg/ml/hr in older patients). Clearance rates also reflected the influence of age, with a rate of 7.40 ml/min/kg in younger patients versus 4.41 ml/min/kg in older children. The average elimination half-life for the entire study population was 4.7 hours, with no differences observed between age groups.

A larger multidose study of 205 children ages 2 months to 13 years provided similar results.[19] Clearance rates in this trial were 6.0 ml/min/kg for the children < 5 years and 4.0 ml/min/kg for the older children. Based on these results, the authors of the two trials suggest that children under the age of 5 years may require an approximately 30% larger dose to achieve desired serum concentrations.

Drug Interactions

The only clinically significant drug interaction with gabapentin is a reduction in its bioavailability by concurrent administration of aluminum and magnesium hydroxide antacids such as Maalox®. Gabapentin should be taken at least 2 hours following an antacid dose. It has been reported that coadministration of gabapentin and naproxen may increase gabapentin absorption by 12-15%, but the clinical significance of this change appears to be minimal. In a case report, administration of a 60 mg controlled-release oral morphine tablet 2 hours prior to a gabapentin dose increased the area under the gabapentin AUC by 44%. The clinical significance and reproducibility of this interaction has not been determined. Gabapentin does not interact with other anticonvulsants. There is no need to adjust the dosages of other anticonvulsants when adding gabapentin.[2,3]

Adverse Effects

The most commonly reported adverse effects associated with gabapentin in premarketing trials of children 3-12 years of age were somnolence (8% of patients), nausea and/or vomiting (8%), behavioral or neuropsychiatric adverse effects (1-6%), fever or infection (3-10%), dizziness (2.5%), and weight gain (4%). For comparison, the most frequently observed adverse effects in adults have been somnolence (19%), dizziness (17%), ataxia (13%), and fatigue (11%). Myoclonus, while rarely observed during clinical trials, has been reported in up to 3-5% of adult patients during postmarketing surveillance. In both adult and pediatric clinical trials, 5 to 7% of patients withdrew because of adverse effects.[2,3,6]

The development of adverse behavioral effects after gabapentin use appears to be considerably more common in children than adults. These symptoms, typically mild to moderate in severity, have included emotional lability and behavioral problems (6% of children in clinical trials), hostility or aggression (5.2%), hyperkinesia, restlessness, or hyperactivity (4.7%), and thought disorders such as difficulty concentrating and poor school performance (1.7%). A reduction in dose has produced a resolution of symptoms in most patients; however, some children have required discontinuation of therapy.[20-23]

Although it has been suggested that larger gabapentin doses (> 25 mg/kg/day) and rapid dose escalation may be linked to the development of adverse behavioral effects, some children have developed symptoms at relatively low doses. It is known that children with pre-existing attention deficit disorder, developmental delays, or other learning disabilities are more likely to experience these adverse effects. Families should be aware of the potential for these adverse effects and instructed to observe the patient for any behavioral changes.[23]

Product Availability

Gabapentin is available as both brand and generic products. Neurontin® (Parke-Davis/Pfizer), is available as 100, 300, and 400 mg capsules, 600 and 800 mg tablets, and a 250 mg/5 ml oral solution. The oral solution must be refrigerated. Generic gabapentin products will soon be available from Eon Labs and Purepac.

Dosing Recommendations

Children under 12 years of age with epilepsy should begin therapy with a gabapentin dose of 10 to 15 mg/kg/day, given in three divided doses. Doses may be increased by 10 mg/kg/day increments every 1-3 days. Based on the trials conducted to date, the usual effective dose of gabapentin in children 3 to 4 years of age is 40 mg/kg/day. In children 5 years of age or older, the usual effective dose is 30 mg/kg/day. The same dosing range has been used for treating neuropathic pain in children. Gabapentin may be given with or without food.[3-6]

Maintenance doses of up to 50 mg/kg/day have been administered to children in clinical trials without adverse effects. Some authors have suggested titrating to as high as 100 mg/kg/day in children with refractory seizures; however, the

utility of these high-dose regimens is often limited by the development of adverse effects.[1,6] In adults, the recommended starting dose is 300 mg given three times daily. In patients with epilepsy, the effective dose of gabapentin ranges between 900 to 1,800 mg/day. In patients with neuropathic pain, higher doses of 1,800 to 4,200 mg/day may be required.[3,8]

Summary

Gabapentin is a novel anticonvulsant with significant analgesic properties. Its use in the pediatric population continues to increase, particularly in the treatment of neuropathic pain. While it is generally well tolerated, there are still concerns over its potential adverse effects on behavior. As its use increases, longitudinal studies should begin to better address the benefit-to-risk profile of gabapentin use in children.

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Pharmacology Literature Review

Enalapril Dose-response Study

The efficacy and safety of enalapril were determined in this study of 110 children. As anticipated, change in blood pressure was strongly correlated with dose, regardless of age, gender, race, or Tanner stage. Wells T, Frame V, Soffer B, et al. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension. **J Clin Pharmacol 2002;42:870-80.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/27/02:

1. Midodrine (ProAmatine®) was added to the Formulary for the treatment of symptomatic orthostatic or intradialytic hypotension.
2. Voriconazole (Vfend®) was added for the treatment of invasive aspergillosis and resistant fungal infections.
3. Amphotericin B lipid complex (Abelcet®) replaced liposomal amphotericin B on the Formulary because of reduced cost.
4. A review of oral 3rd generation cephalosporins was completed, but no changes were made.
5. Papain/urea/chlorophyllin ointment (Panafil®) was added for debridement and wound healing.
6. Prazosin was deleted from the Formulary.
7. Tamsulosin (Flomax®) was rejected.

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