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Clobazam: A New Option for Children with Refractory Seizures

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On October 24, 2011, the Food and Drug Administration (FDA) approved clobazam as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older. Clobazam, a benzodiazepine antiepileptic, has been used in countries outside the US for more than 30 years, producing an overall reduction in seizure frequency of approximately 60% in clinical trials. It received orphan drug status in the US in 2007, but was not readily available.^{1,2} This issue of *Pediatric Pharmacotherapy* will review the use of clobazam in children with refractory seizures, including recommendations for dosing and monitoring.

Mechanism of Action

Clobazam is a 1,5-benzodiazepine, structurally different than traditional 1,4-benzodiazepines (e.g. diazepam). It has an amide group in the fourth and fifth position, rather than an imine group. Benzodiazepines bind between the alpha and gamma subunits of the GABA receptor, potentiating GABA-mediated inhibition of neurotransmission. The 1,5-benzodiazepines are less lipophilic and acidic than the 1,4-benzodiazepines, changing their distribution characteristics and potentially resulting in less sedation and a slower development of tolerance.

Pharmacokinetics

Clobazam is rapidly absorbed after oral administration, with a time to maximum concentration of 0.5-4 hours in adults and a bioavailability of 100%. Administration with food does not affect the rate or extent of absorption. Clobazam is widely distributed throughout the body, with an apparent volume of distribution of 100 L in adults. It is 80-90% protein bound. It is metabolized by CYP3A4 to active N-desmethylclobazam, and to a lesser degree by CYP2C19, CYP2C18, and CYP2B6. Plasma concentrations of N-desmethylclobazam are up to 5 times that of the parent compound. It is estimated that the potency of the metabolite is approximately 20-40% that of clobazam. In an observational study of 28 adults, Kinoshita and colleagues found that seizure control correlated

with the ratio of plasma N-desmethylclobazam concentration to dose per kg ($p = 0.0167$).³

N-desmethylclobazam undergoes further metabolism through CYP2C19. The mean elimination half-life of clobazam has ranged from 36-42 hours in adults. The mean half-life of N-desmethylclobazam is approximately 71-82 hours. Patients who are CYP2C19 poor metabolizers, those carrying the *2 allele (CYP2C19*1/*2), have a reduced ability to clear the active metabolite. This difference may result in N-desmethylclobazam concentrations 3- to 5-fold higher than patients who are extensive metabolizers. Dosage reduction is recommended for these patients to avoid toxicity.⁴⁻⁶

Clinical Studies

A variety of studies have been published documenting the efficacy and safety of clobazam in pediatric patients.⁷⁻¹⁶ Beginning with Munn and colleagues in 1988, clobazam has been found to be an effective adjunctive therapy for children with refractory seizures.⁷ This group from Nova Scotia, Canada reported their experience with clobazam in 27 children (mean age 9 years). Eighty-five percent of the children had multiple seizures on a daily basis; 93% had neurologic impairment. The study patients had received an average of six other antiepileptics prior to enrollment. Clobazam produced a reduction in seizure frequency of at least 75% in 41% of the children. Fifteen percent became seizure-free. Tolerance occurred in 26% of the patients.

The first large-scale prospective study of clobazam as monotherapy in children was conducted by the Canadian Study Group for Childhood Epilepsy.¹⁰ In 1998, the group published the results of their 15-center, randomized, double-blind study comparing clobazam to standard monotherapy in children with refractory seizures. A total of 235 children between 2 and 16 years of age were randomized to receive clobazam, beginning at 0.5 mg/kg/day, or carbamazepine, beginning at 10 mg/kg/day. Children who had a prior history of failing treatment with carbamazepine were randomized

to clobazam or phenytoin, beginning at 5 mg/kg/day. Dose adjustments were made by the patient's neurologist.

The authors found no difference in the primary endpoint, the number of patients remaining on therapy at 1 year (54.6% of the clobazam patients versus 56.9% in the carbamazepine and phenytoin groups combined). There was also no difference in the percent of children who were seizure-free for the entire year: 23% of the clobazam patients, compared to 25% of the patients receiving carbamazepine and 11% of those on phenytoin. The average maximum dose of clobazam in this study was 0.6 mg/kg/day, similar to that in earlier studies. Adverse effects were also similar among the groups. Tolerance developed in 7.5% of the children receiving clobazam.¹⁰

In 1999, these authors published an additional paper using a subset of patients from their 1998 study to compare the cognitive and behavioral effects of clobazam and standard monotherapy.¹¹ A total of 41 children were evaluated 6 weeks and 12 months after initiation of therapy. The authors found no differences in neurocognitive assessments of intelligence, memory, attention, psychomotor speed, and impulsivity between clobazam and either standard therapy. In the clobazam group, scores on the Nonverbal Selective Reminding Test improved over the 12 month treatment period. Other test scores remained stable. None of the testing measures declined over the study period. There was no significant difference in the number of children demonstrating behavioral adverse effects (six children taking clobazam compared to five receiving standard monotherapy).

Two additional papers have been published from the State University of Campinas, Brazil.^{12,13} In 2006, Silva and colleagues conducted a retrospective review of clobazam as adjunctive therapy in 97 children treated in their clinic.¹³ All patients were between 1 and 17 years of age and had seizures associated with underlying encephalopathy. Twenty-six patients had Lennox-Gastaut syndrome. All patients were taking other antiepileptics and had been treated with at least three other agents prior to receiving clobazam. Treatment was initiated with 5 mg once daily at bedtime and increased as needed up to 30 mg given twice daily (average final dose 37.5 mg/day). Improvement was documented in 54.5% of the patients. Eleven percent had a reduction in seizure frequency of at least 75%, with nine becoming seizure-free. Although 41%

experienced adverse effects, most were mild. Only 11 patients discontinued therapy because of an adverse effect. Over 85% of the children remained on clobazam at 12 months.

In 2010, Kalra and colleagues at the All India Institute of Medical Sciences reported their experience with clobazam in 88 children (ages 7 months to 12 years) with refractory epilepsy.¹⁴ Most of the children had daily seizures and were on at least two other antiepileptics. The average maintenance dose was 1 ± 0.2 mg/kg/day, with a range of 0.3-2 mg/kg/day. Complete seizure control was reported in 60.2%. Only four patients failed to show improvement. Tolerance developed in 5.6% by 3 months and 10.2% by 6 months. Adverse effects were reported in 26% of patients, but most were mild. Sedation was the most frequently reported adverse effect, occurring in 11.3%. Only three discontinued therapy because of an adverse effect.

A similar rate of patient retention was shown by Mills and colleagues at the University of Nottingham.¹⁵ In their 2011 retrospective study, the authors analyzed results from 194 children (0.1-15.1 years of age) treated for refractory seizures over an 8-year period. Clobazam, topiramate, and lamotrigine were all used as second-line therapies. The mean clobazam maintenance dose was 0.7 mg/kg/day, with a range of 0.12-3.5 mg/kg/day. Fifty-one percent of patients remained on clobazam for more than a year. In comparison, 37% of patients started on topiramate and 69% of those given lamotrigine were still on therapy at 1 year. Forty-three percent of the clobazam patients, 35% of the topiramate group, and 44% of the lamotrigine group experienced at least a 50% reduction in seizure frequency. The authors concluded that both clobazam and lamotrigine were second-line therapies likely to produce significant benefit.

The approval of clobazam in the US was based on two prospective randomized, double-blind clinical trials supported by the manufacturer.^{2,16} In the first study, 238 patients (2-54 years of age) with Lennox-Gastaut syndrome received clobazam or placebo for 15 weeks (a 3-week titration followed by 12 weeks at maintenance).² Patients were divided into two groups, those 30 kg or under and those over 30 kg. The groups were then randomized to placebo or clobazam at one of three target maintenance doses: low, medium, and high (5, 10, or 20 mg/day for the lower weight group and 10, 20, or 40 mg/day for the higher weight group). The weight groups were combined for analysis. All doses of

clobazam produced a significant reduction in seizure frequency. The mean percent reduction from baseline in the number of drop seizures per week was 12.1 for the placebo group, 41.2 in the low-dose group ($p < 0.05$), 49.4 in the medium-dose group ($p < 0.01$), and 68.3 in the high-dose group ($p < 0.01$).

The second study was a randomized, double-blind, dose-ranging study conducted in 68 patients with Lennox-Gastaut syndrome between the ages of 2 and 26 years (median age 7.4 years).¹⁶ Patients were randomized to receive clobazam at a maintenance dose of 0.25 mg/kg/day up to 10 mg/day (low-dose) or 1 mg/kg/day up to 40 mg/day (high-dose). After a 4-week baseline evaluation, drug was administered over a 3-week titration and a 4-week maintenance period. The mean number of drop seizures decreased from 141 ± 188 to 91 ± 122 in the low-dose group, resulting in a 12% reduction ($p = 0.0162$). The high-dose group had a mean decrease from 207 ± 229 drop seizures at baseline to 32 ± 57 at final assessment, producing an 85% reduction ($p < 0.0001$). More patients in the high-dose group were seizure-free at the end of the study (22% versus 6%), but the difference was not statistically significant ($p = 0.06$). There was a high rate of adverse effects (over 80% in each group), but most were mild. The most commonly reported were somnolence, lethargy, sedation, hypersalivation, and constipation. Three patients in the low-dose group and six in the high-dose group discontinued treatment because of adverse effects.

Contraindications and Precautions

Like other antiepileptics, clobazam carries a black box warning alerting health care providers to the risk for depression and suicidal thoughts in patients taking these medications. The risk for these effects in patients taking clobazam has not yet been thoroughly evaluated.^{1,2}

Adverse Effects

The most frequently reported adverse effects with clobazam in clinical trials have been sedation (in 26% of patients compared to 15% of placebo controls), fever (13% compared to 3%), lethargy (10% compared to 5%), drooling (9% compared to 3%), aggression (8% compared to 5%), vomiting (7% compared to 5%), constipation (5% compared to 0), and irritability (7% versus 5%). Other adverse effects reported in at least 5% of patients included dysphagia (2%), changes in appetite (3%), ataxia or dysarthria (3-5%), insomnia (5%), and cough

(5%). Rates of infections were similar between patients receiving clobazam or placebo.^{1,2}

Hypersensitivity reactions appear to be rare, but rash, Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis have been reported after clobazam use. Causation has not been established in these case reports, but health care providers should be aware of the potential risk. Ertam and colleagues recently described a 4-year-old boy who developed SJS 10 days after clobazam was added to his prior regimen of valproic acid and lamotrigine.¹⁷

Drug Interactions

Clobazam is a weak inducer of CYP3A4 and may reduce concentrations of drugs metabolized via this pathway. Concentrations of hormonal contraceptives may be reduced, making them less effective. It is recommended that patients taking this combination use an additional form of contraception. Clobazam decreases midazolam concentrations when the drugs are given concomitantly, reducing the maximum plasma concentration by 24% and increasing concentrations of the 1-hydroxymidazolam metabolite 2-fold. Based on the relatively small change, no dosage adjustment is recommended. Clobazam inhibits CYP2D6 and may increase concentrations of drugs metabolized by that enzyme. It does not appear to significantly alter the elimination of valproic acid or lamotrigine.

Drugs that inhibit or induce CYP3A4 or CYP2C19 may result in altered concentrations of clobazam or N-desmethyloclobazam. Although no specific recommendations have been proposed, dosage adjustment may be necessary in patients receiving ketoconazole (a CYP3A4 inducer), as well as fluconazole, fluvoxamine, omeprazole, or ticlopidine (CYP2C19 inhibitors). Alcohol increases levels of clobazam by 50% and may produce additive sedative effects. Other antiepileptics that induce CYP3A4 (carbamazepine, phenobarbital, phenytoin), induce CYP2C9 (carbamazepine, phenobarbital, phenytoin, and valproic acid), or inhibit CYP2C9 (felbamate, oxcarbazepine) do not appear to produce significant alterations in clobazam pharmacokinetics.^{1,2}

Availability and Dosing Recommendations

Clobazam (Onfi™, Lundbeck, Inc.) is available in three strengths: 5, 10, and 20 mg. The tablets are packaged in bottles of 100 and should be stored at room temperature. Although clobazam has been approved by the FDA, it is not yet available for purchase in the US. The

manufacturer plans to begin marketing the drug in early January 2012.¹

The recommended dose for initiating clobazam in children weighing 30 kg or less is 5 mg given once daily. After 7 days, the dose may be increased to 5 mg twice daily. A third dose increase to 10 mg twice daily can be made after 14 days of therapy. Patients weighing more than 30 kg may be started on a clobazam dose of 10 mg once daily. Subsequent dose increases can be made at weekly intervals to 10 mg twice daily, and then 20 mg twice daily. Because of the long half-life of clobazam and its metabolite, dosage adjustments should not be made more frequently than weekly. Clobazam may be taken with or without food. The tablets may be crushed and mixed with applesauce for patients unable to swallow them whole.^{1,2}

Patients who are CYP2C19 poor metabolizers are at risk for toxicity due to accumulation of the active metabolite. If this is known prior to the initiation, or if the patient has mild to moderate hepatic impairment, the starting dose should be reduced to half of the recommended amount. Further titration should not be undertaken for at least three weeks. Patients exhibiting significant adverse effects, including somnolence, with routine dosing should be evaluated for elevated N-desmethylclobazam plasma concentrations and/or the presence of the CYP2C19 *2 allele.^{5,6} No dosage adjustment is required for patients with mild to moderate renal impairment. There are no data to guide dosing in patients with severe renal or hepatic impairment.^{1,2}

Abrupt discontinuation of clobazam may result in symptoms of withdrawal, ranging from headache, insomnia, anxiety, and dysphoria to worsening seizures, tremor, nausea, vomiting, blurred vision, hallucinations, anxiety, or other behavioral disorders. Clobazam should be tapered off, with the total daily dose decreased by 5-10 mg/day on a weekly basis.^{1,2}

Summary

Clobazam offers a new option for the treatment of refractory seizures, especially in children with Lennox-Gastaut syndrome. It is generally well tolerated, but like other benzodiazepines, is associated with somnolence and the development of tolerance. Long-term studies are needed to clarify the role of clobazam in pediatrics.

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