Clobazam

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Summary: Catastrophic childhood epilepsies such as infantile spasms (IS), progressive myoclonic epilepsy, and Lennox-Gastaut syndrome (LGS) are rare but debilitating and frequently persist into adulthood. Early, targeted use of medications that have demonstrated efficacy in the management of LGS or its associated epilepsies may simplify the patient's treatment regimen and reduce the incidence of adverse events. Key to the overall benefit to the patient is to maximize seizure control while minimizing adverse effects, especially behavioral and cognitive problems. Clobazam has demonstrated clinical benefit and has been administered safely in more than 50 European studies in which data were reported on greater than 3000 pediatric and adult patients with epilepsy, 300 of whom were diagnosed with LGS; therefore, its use is now being investigated in the U.S. This review will explore the use of clobazam in the treatment of epilepsy, particularly with regard to its potential benefit in LGS. Though not currently approved for use in the U.S., a program is underway to gain Food and Drug Administration approval for the treatment of pediatric and adult patients with refractory epilepsy, specifically in LGS. A phase 2 study will be completed in late 2006 to investigate the safety and efficacy of clobazam as adjunctive therapy in 68 pediatric and adult patients with LGS. **Key Words:** Catastrophic childhood epilepsy, refractory epilepsy, treatment resistant epilepsy, epilepsy treatment, Lennox-Gastaut syndrome, clobazam.

INTRODUCTION

Epilepsy is a common medical disorder with a cumulative incidence of 3% in the general population.[1] A significant minority of patients with epilepsy develop catastrophic variants of the disorder. Catastrophic childhood epilepsies such as infantile spasms (IS), progressive myoclonic epilepsy, and Lennox-Gastaut syndrome (LGS) are rare but debilitating and frequently persist into adulthood.[2]

Lennox-Gastaut syndrome occurs in 3% to 10% of all childhood epilepsies and is characterized by a clinical triad that includes multiple types of epileptic seizures, severe neurocognitive and/or behavioral disturbance, and specific electroencephalogram abnormalities.[2] Onset typically occurs between 3 and 10 years of age and is heterogeneous. For example, patients may premorbidly appear to be without neurological abnormality, exhibit early developmental delay, or develop LGS subsequent to other epilepsies, most commonly IS.[2] The etiology may be cryptogenic or symptomatic with the latter accounting for approximately 75% of all LGS cases.[3] Patients with LGS most frequently present with generalized tonic, atonic, myoclonic, or atypical absence seizures but may also exhibit other seizure types; the disorder is chronic and has an associated mortality of 5% to 17%. Seventy-five to 90% of children with LGS are affected by mental retardation, while comorbid behavioral and sleep disturbances are common as well.[4]

Patient evaluation should include a range of structural (i.e., detailed neuroimaging), electrophysiological, developmental, and metabolic studies, as well as neuropsychological assessment.[4] Accurate diagnosis and treatment may improve cognitive and behavioral dysfunction associated with LGS.[5] Early, targeted use of medications that have demonstrated efficacy in the management of LGS or its associated epilepsies may simplify the patient's treatment regimen and reduce the incidence of adverse events. Key to the overall benefit to the patient is to maximize seizure control while minimizing adverse effects, especially behavioral and cognitive problems. While true in any epilepsy, this maxim is especially relevant for children throughout their development, particularly those already challenged by cognitive deficits. Several pharmacologic therapies have been used to treat LGS. Current pharmacologic therapies consist of benzo-

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diazepines, valproate, topiramate, levetiracetam, zonisamide, vigabatrin, lamotrigine, and /or felbamate.[2] Nonpharmacologic treatments have also been used for LGS, predominantly involving vagus nerve stimulation and the ketogenic diet, which have reduced the need for corpus callosotomy.[5]

CLOBAZAM OVERVIEW

History and regulatory status

Current pharmacotherapy agents often fail to substantially ameliorate seizures in LGS. In the U.S, where clobazam is not currently available, the Food and Drug Administration (FDA) has approved three antiepileptic drugs (AEDs) which have demonstrated clinical efficacy for the treatment of LGS: felbamate, lamotrigine, and topiramate. Each of these drugs is effective in some, but not all, patients and bears the risk of tolerance in some initially responsive patients. In addition, all three drugs are associated with significant adverse events in some patients. Clobazam has demonstrated clinical benefit and has been administered safely in more than 50 European studies in which data were reported on greater than 3000 pediatric and adult patients with epilepsy, 300 of whom were diagnosed with LGS[6]; therefore, its use is now being investigated in the U.S. This review will explore the use of clobazam in the treatment of epilepsy, particularly with regard to its potential benefit in LGS. Though not currently approved for use in the U.S., a program is underway to gain FDA approval for the treatment of pediatric and adult patients with refractory epilepsy, specifically in LGS. A phase 2 study will be completed in late 2006 to investigate the safety and efficacy of clobazam as adjunctive therapy in 68 pediatric and adult patients with LGS.

Current indications and clinical targets

Clobazam is a 1,5-benzodiazepine that possesses potent anticonvulsant properties and demonstrates anxiolytic properties as well.[7] Clobazam was approved in France in 1974 as a treatment for anxiety and/or the adjunctive treatment of epilepsy and is currently available in over 100 countries, including most recently Japan, where it was approved in the treatment of LGS and other refractory epilepsies.[8] Clobazam has not been evaluated or approved by the FDA in the U.S.

Preclinical studies

The efficacy of clobazam as a broad-spectrum anticonvulsant agent has been demonstrated in multiple pharmacology studies with various animal models of induced and inherited seizures, where clobazam was found to be at least equipotent to other benzodiazepines.[9-12] With regard to the safety of clobazam, toxicological evaluation of the adverse effects of clobazam and its metabolites has been conducted in mice,[13-15] rats,[16-21] guinea pigs,[22] rabbits,[23] dogs,[24-28] and nonhuman primates.[29,30] Repeated, daily, supraphysiologic doses exceeded the maximum target daily dose of 1 mg/kg/day in humans by factors of 1000, 80, and 20, respectively, in rats, dogs, and monkeys. Lifetime exposures to 100 times the human exposure were assessed in mice and rats.[31,32] Given that lower protein binding in rats and monkeys provided substantially greater exposure to the active drug than is achieved via comparable dosing in humans, it appears that the risk for adverse effects from acute overdosing is low, owing to oral median lethal doses ranging from greater than 100 to greater than 5000 mg/kg.[6,16,18]

At doses 200-times the human dose (i.e., 200 mg/kg/day), developmental and reproductive toxicity studies conducted in mice,[33] rats,[34,35] and rabbits[36] failed to reveal adverse effects of clobazam on fertility and perinatal development. The absence of a teratogenic potential for clobazam was further confirmed by two additional developmental toxicity studies in Sprague-Dawley rats that utilized maximal doses of 400 times higher than the recommended human dose (100 or 400 mg/kg/day).[36] Pregnant rabbits treated with up to 100 times the human dose (100 mg/kg/day) had an increase in fetal resorptions at the highest dose.[36] While there was a low incidence of variable but common developmental anomalies in all dose groups, there was no evidence to support a relationship to clobazam dosing. Notably, the incidence of these anomalies was consistent with the historical control data from the laboratory performing the study.[36] Overall, these studies indicate that clobazam does not induce birth defects; however, the potential for developmental toxicity at doses 100-fold greater than that given to humans cannot be excluded.

Clobazam does not lead to mutagenic or clastogenic changes, with or without metabolic activation, as demonstrated by a comprehensive battery of genotoxicity assays.[37-39] Lifetime exposure of clobazam at 100 times (100 mg/kg/day) the human dose in mice and rats confirmed that clobazam is not carcinogenic.[31,32] Miyawaki et al.[40] observed perturbation in thyroid hormone and thyroid stimulating hormone levels in male Sprague-Dawley rats following up to 4 weeks of 400 mg/kg/day doses. However, Capen[41] determined that the associated modest increase in thyroid follicular cell tumors was developed via secondary oncogenetic mechanisms peculiar to the gender and species; experts in toxicology have determined that clobazam is not a risk for human thyroid cancer. Withdrawal effects were observed when animals were dosed with clobazam or a main metabolite; however, clobazam does not demonstrate addictive properties.[6]

Pharmacokinetics

The pharmacokinetic properties of clobazam have been studied over the past 30 years. Clobazam is rapidly

absorbed following oral administration with 87% bioavailability with maximum concentrations achieved between 1 to 4 hours[42,43]; the absorption rate is slowed but not generally affected by food intake. [44,45] Studies in children suggest that young patients may metabolize clobazam more rapidly than adults by 53% to 69%.[46-48] In adult patients with epilepsy, the clobazam elimination half-lives are faster than in healthy volunteers (at 12 and 24 h, respectively); the elimination half-life in children with epilepsy is approximately 16 hours.[49] *N*-desmethylclobazam (NCLB) is its pharmacologically active metabolite and may substantially contribute to the efficacy and safety profile of clobazam.[50] The 42-hour half-life of NCLB is two times longer in duration than that of clobazam with an eightfold greater steady-state plasma concentration than clobazam.[51] Clobazam and NCLB are both hepatically metabolized by cytochrome P450 2C19 (CYP2C1). Other substrates for CYP2C1 may affect clobazam and NCLB metabolism. For example, carbamazepine, phenytoin, and phenobarbital may reduce clobazam concentrations by approximately 50%,[52] while cimetidine has been shown to increase the plasma half-life by approximately 10%.[53]

The presumed major mechanism of action for clobazam is similar to that of the 1,4-benzodiazepines, acting on benzodiazepine receptors to potentiate the inhibitory neurotransmitter GABA, on voltage sensitive calcium ion conductance, and on sodium channels.[54,55] Unlike all other benzodiazepines, which have a 1,4 structure, clobazam is the only 1,5-benzodiazepine available.[56] Its nitrogen atoms occupy the 1 and 5 position, a keto group is placed in the 4 position, and the remainder of the molecule is analogous to diazepam.[56] It was synthesized in 1966 as part of a program to improve efficacy and reduce side effects of sedation and hypotonia of the 1,4-benzodiazepines. The antiepileptic effects of clobazam have also been associated with its involvement in allosteric activation of $GABA_A$, hippocampal up-regulation of the GABA transporter (GAT) GAT3, and augmentation of GAT1.[55] Clobazam demonstrates reduced affinity for the ω1-allosteric binding site on the $GABA_A$ receptor and greater selective affinity for the ω2 site as compared with the 1,4-benzodiazepines; which has been implicated as the mechanism responsible for its relatively reduced sedative effects and increased anticonvulsant properties.[57-59]

Double-blind and open-label studies of clobazam in adult patients with LGS have utilized dosages of 0.05 to 3.8 mg/kg/day. Maximally efficacious average doses achieved are approximately 1.9 mg/kg/day with the majority of studies reporting administering clobazam at dosages $\leq$1.5 mg/kg/day.[48,60,61] Generally, it appears that a minimum therapeutic effect of clobazam can be achieved in adults with a target low dose of 0.25 mg/kg/day twice a day, and that a target high dose of 1 mg/kg/day (or 40 mg/day) twice a day is usually tolerable and may provide effective seizure reduction or elimination. The most efficacious clobazam dosage range identified in pediatric studies has been approximately 0.5 to 1.0 mg/kg/day twice a day.[47] This suggests that a minimum therapeutic effect of clobazam in children with LGS can be achieved with a target low dose of 0.25 mg/kg/day twice a day and a target high dose of approximately 1.0 mg/kg/day twice a day based on efficacy and tolerability.

Clinical studies

Data from more than 300 patients in 20 studies has contributed to an understanding of the effectiveness of clobazam in the treatment of LGS. Examination of the subpopulations of LGS patients in initial groups of patients with refractory epilepsies revealed seizure reduction ranges of 50% to 100% in $\geq$50% of patients.[62-64] Seizure types in these studies with the highest efficacy included atonic seizures and bilateral myoclonus.[62-65] Much of the data regarding the efficacy of clobazam in patients with LGS comes from two retrospective reviews and several small, open-label studies. The results of 80 patients with LGS were specifically reported in eight of the open-label studies, in which 62.5% of patients reported improvement with clobazam therapy with 56.3% reporting $\geq$50% decrease in seizure frequency.[8,48,66-71] Of the studies that included reports of seizure freedom, it is notable that more than 10% of treatment refractory patients achieved complete cessation of their seizure activity.[7] In the remaining open-label studies (for which results of LGS patients were not reported separately from those of other patients), efficacy results across all patient types reflect seizure-free rates from 31% to 68% with an additional 26% to 45% of patients experiencing a $>$50% decrease in seizure frequency.[7,47,72-77] With regard to the long-term effectiveness of clobazam in LGS, up to 42% of patients have maintained clinical benefits for more than 1 year[67,68]; with seizure freedom reported in 7% for periods $>$6 months.[48]

The Canadian Clobazam Cooperative Group[7] reported the efficacy results of 877 patients, including 45 patients with LGS, based on how many seizure types were experienced by each patient. Forty-three percent of patients with a single seizure type experienced a $\geq$50% reduction in seizure frequency, including 13% who became seizure-free. Of patients with multiple seizure types, 61% had a $\geq$50% reduction in the frequency of one or more seizure types, and nearly 40% of patients had a $\geq$50% reduction in the frequency of all their seizure types, including 14% of patients who achieved seizure freedom across all seizure types. Overall, these data suggest that clobazam may play a significant role in the treatment of patients with LGS.

The effectiveness of clobazam in patients with epilepsy types other than LGS has been reported in 32 publications, including more than 1300 adult and pedi-

atric patients. The patients presented with a broad range of epilepsy types, many with intractable seizures, including partial, partial with secondary generalization, generalized tonic–clonic, and myoclonic. Results from multiple double-blind studies,[56,78-87], open-label studies,[52,54,61,88-103] and retrospective reviews[7,104,105] have suggested that clobazam is equally as effective as monotherapy with phenytoin or carbamazepine in childhood epilepsies that include partial seizures, partial seizures with secondary generalization, and some primary generalized tonic-clonic seizures.[80] Importantly, effectiveness was demonstrated at one year of treatment, a difficult and unusual endpoint. The proportion of patients developing tolerance to clobazam (7.5%) was found to be comparable with tolerance rates in patients treated with carbamazepine (4.2%) or phenytoin (6.7%).[80]

The safety profile of clobazam has been established in approximately 50 clinical studies in more than 3000 adult and pediatric patients with epilepsy. Clinical studies have indicated that the adverse event (AE) profile of clobazam is consistent with the class of benzodiazepines; however, AEs associated with clobazam use are often less severe than those associated with the 1,4-benzodiazepines. Approximately 40% of patients experience transient AEs of mild to moderate severity such as the following: dose-related sedation/drowsiness, dizziness, and/or ataxia; these AEs are most often cited as reasons for dosage reduction or discontinuation of clobazam.[62,63,106] Notably, the sedative effects of clobazam are 1000% less than those of the 1,4-benzodiazepines and clobazam has no known addictive potential.[54] Behavioral abnormalities and drooling are also reported, although drooling has been noted as less pervasive than the 1,4-benzodiazepines.[62,63,94,106] Positive psychotropic effects of clobazam have also been reported in numerous studies that found associated decreases in anxiety and improved alertness–concentration.[47,52,70,71,74,75,94,95,99,101,107] An average of 9% of patients (range, 1–26%)[93,105] experienced worsening of seizures during clobazam therapy as demonstrated by an increase in the frequency and/or duration of seizures for any reason; responsiveness to clobazam was not found to be associated with differences in neurological status, seizure type, or comedication.[93] Worsening of seizures in these studies could have been due to reductions of concomitant AEDs, tolerance, or factors unassociated with clobazam such as intercurrent illness.

No clinically significant laboratory abnormalities have been associated with clobazam. Serious AEs have been infrequently reported in clinical studies, but have included hepatic failure,[79] status epilepticus (SE),[56,65,80,93] and death.[93] The rarity of these events is evidenced by the fact that of the greater than 1.1 million patient years of exposure documented from November 1994 to February 2004, hepatic failure, SE, and/or mortality were observed in a total of five patients.[6] Overdose has not been reported in any clinical study. In the majority of studies, clobazam was used as adjunctive therapy with a variety of other AEDs and was very well tolerated. Drug–drug interactions are generally minimal. Clobazam has been associated with increased carbamazepine levels of dubious clinical significance.[88] Clobazam may inhibit valproic acid metabolism and clinicians are advised to watch for valproic acid toxicities when adding clobazam in patients who are already on valproic acid therapy.[108,109] In sum, the clinical data available suggest that the risk of novel serious adverse effects is very low; known adverse effects are usually not serious, are predictable, and are generally dose-related and reversible.

Ongoing clinical trials

An investigative new drug application (IND) was opened to evaluate the safety and efficacy of clobazam as adjunctive therapy in 68 pediatric and adult patients with LGS in 2005 with a randomized, double-blind, phase 2 dose-finding study that will be completed in 2006. Because the range of doses in previous trials ranged from approximately 0.2 to 1.5 mg/kg/day with increasing AEs over 1.0, this study was established to determine a safe and effective dose for a definitive phase 3 efficacy and safety trial between 0.25 and 1.0 mg/kg/day. Patients received target clobazam doses of 0.25 mg/kg/day (or a maximum dose of 10 mg/day) or 1.0 mg/kg/day (or a maximum dose of 40 mg/day) with the tablet formulation. The study consisted of a four-week baseline phase, three-week titration phase, a four-week maintenance phase, and, for subjects not continuing into the open-label extension study, up to a three-week taper/follow-up phase. Safety, efficacy, and pharmacokinetic endpoints will be assessed in order to establish an adequate dose for phase 3 clinical studies of clobazam. Population pharmacokinetic data will be used to define further the pharmacokinetics of clobazam in the pediatric and adult subjects with LGS. Poststratification (i.e., modeling) will be used to elicit the effects of demographics and other factors including CYP genotype and concomitant medications including inducers and or inhibitors of CYPs. The clinical development program of clobazam will also address the pharmacokinetics of clobazam in renal and hepatic insufficiency, as well as the effect of food on bioavailability.

Lennox-Gastaut syndrome poses a significant treatment challenge. More effective and better-tolerated treatment options are needed for this population of medically intractable epilepsy patients. Many studies have concluded that clobazam is an effective AED against a broad spectrum of seizure types with an acceptable safety profile; it has been shown to reduce and, in some patients, eliminate difficult to treat seizure types such as atonic seizures. It has also been shown to maintain that effectiveness over time in many patients. Available data there-

fore suggest that clobazam may have utility in the treatment of LGS and that further clinical trials to establish definitive efficacy and safety in the U.S. population are warranted.

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