Pediatric Neurology 51 (2014) 60–66

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Clobazam: Effect on Frequency of Seizures and Safety Profile in Different Subgroups of Children With Epilepsy

Jacquelyn Klehm [a,*], Sigride Thome-Souza MD, PhD [a,b], Iván Sánchez Fernández MD [a,c], Ann M. Bergin MD [a], Jeffrey Bolton MD [a], Chellamani Harini MD [a], Navah E. Kadish PhD [a], Mark Libenson MD [a], Jurriaan Peters MD [a], Annapurna Poduri MD [a], Alexander Rotenberg MD, PhD [a], Masanori Takeoka MD [a], Blaise Bourgeois MD [a], Tobias Loddenkemper MD [a]

[a] *Epilepsy and Clinical Neurophysiology, Boston Children's Hospital, Boston, Massachusetts*
[b] *Psychiatry Department, Clinics Hospital of University of Sao Paulo, Sao Paulo, Sao Paulo, Brazil*
[c] *Department of Child Neurology, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Catalonia, Spain*

ABSTRACT

BACKGROUND: Clobazam has been used in clinical practice as an adjunctive treatment for diverse seizure types and epilepsy syndromes. We evaluated the efficacy and safety of clobazam in a large sample of patients with refractory epilepsy at a tertiary pediatric center. **METHODS:** We retrospectively reviewed patients treated with clobazam between January 2001 and July 2013 who had a follow-up visit at least one month after starting clobazam. Response was defined as ≥50% reduction in seizure frequency compared with baseline seizure frequency during the 3 months before the introduction of clobazam. We examined the relationship between dose range and response rate. **RESULTS:** Four-hundred twenty-five patients were prescribed clobazam, of whom 300 (median age 9.1 years, interquartile range 4.7-13.3 years) had follow-up data greater than 1 month. Median follow-up was 5 months (interquartile range 3-11 months). Response to treatment with clobazam was observed in 203 of 300 (67.7%) patients, of whom 84 (28%) became seizure-free. The median starting dose was 0.2 (interquartile range 0.13-0.33) mg/kg/day with a target dose of 0.48 (0.26-0.80) mg/kg/day. Twenty-seven (9%) patients discontinued clobazam, 16 (59.3%) because adverse effects, 10 (37%) because of a lack of efficacy, and one (3.7%) because of a combination of adverse effects and lack of efficacy. The most common adverse effects were tiredness in 44 of 300 (14.6%) and mood or behavioral changes in 23 (7.7%). **CONCLUSIONS:** Clobazam is a well-tolerated antiepileptic drug with good response rates in pediatric patients with refractory epilepsy.

Keywords: epilepsy, refractory epilepsy, pediatric, seizure, efficacy

Pediatr Neurol 2014; 51: 60-66

Introduction

Clobazam is a 1,5-benzodiazepine with marked anxiolytic and anticonvulsant properties.[1] It acts as a partial agonist on the gamma-amino butyric (GABA) receptor complex, similar to other benzodiazepines. However, unlike 1,4-benzodiazepines, it is selective for the ω-2 subunit.[2] When clobazam binds to the $GABA_A$ receptor, it causes an influx of chloride, leading to membrane hyperpolarization and an increase in inhibitory postsynaptic potentials, a mechanism also observed with other benzodiazepines.[3-5]

Preferred epilepsy treatment consists of monotherapy with a single antiepileptic drug (AED) at the minimally effective dose, up to the maximum tolerated dose.[6] However, many patients require more than one AED, and in some reports 30% of patients continue to have seizures despite drug treatment.[6,7] Clobazam is a common

Article History:
Received October 10, 2013; Accepted in final form January 8, 2014
* Communications should be addressed to: Dr. Klehm; Research Assistant; Division of Epilepsy and Clinical Neurophysiology; Fegan 9; Boston Children's Hospital; 333 Longwood Avenue; Boston, MA 02115.
E-mail address: jacquelyn.klehm@childrens.harvard.edu

0887-8994/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2014.01.025

medication choice for drug-resistant seizures. Previous studies have shown that clobazam is an effective adjunctive therapy for partial and generalized seizures and status epilepticus,[8] febrile seizures,[9,10] reflex seizures,[11] and hyperekplexia.[12]

Treatment of epilepsy may require polytherapy and high doses of medication, which frequently are associated with side effects. Clobazam has less affinity than 1,4 benzodiazepines for the ω-1 receptor and ω-5 subunit of the GABA receptor, which are known to be associated with sedation and cognitive changes.[5] The most common adverse events leading to the discontinuation of clobazam are lethargy, somnolence, aggression, ataxia, insomnia, and fatigue.[13] The prevalence of dosage-related adverse events is still unknown.[4,13] Increase in seizures, worsening of seizures, or development of new seizure types have been reported in 5% to 13% of patients.[14] Most reported adverse events due to clobazam appear to be less severe than those reported with 1,4-benzodiazepines, whereas a similar level of seizure control is obtained.[13]

Our aim is to describe the use of clobazam in a refractory epilepsy population at a single pediatric center during a long-term period. Our secondary goal is to identify subsets of patients in which clobazam emerged as an effective drug and also to try to define particular treatment regimens associated with better outcomes and/or fewer adverse events.

Methods

Patient selection

We obtained approval from the Boston Children's Hospital Institutional Review Board before the acquisition of data. Patients were identified using the Informatics for Integrating Biology and the Bedside software (Partners Healthcare, https://www.i2b2.org/), using the search terms clobazam, Onfi, and epilepsy. We reviewed all patient charts, including outpatient and inpatient visits, electrophysiology, and neuroimaging examinations for patients who used clobazam for treatment of epilepsy between January 2001 and July 2013. We evaluated details regarding clobazam use, including dose, titration mode, adverse effects, and combinations with other AEDs. Patients who were already initiated on clobazam before being seen at Boston Children's Hospital or who did not return for follow-up at least 1 month after clobazam initiation were excluded from analysis.

Epilepsy classification and seizure control

Epileptic seizures were classified according to International League Against Epilepsy criteria.[15] Responders were defined as patients who experienced a reduction in overall seizure frequency ≥50% at last follow-up compared with baseline. Nonresponders were patients who experienced <50% reduction in overall seizure frequency compared with baseline. Adverse effects and efficacy were evaluated according to information provided by physicians, patients, parents, relatives, and caretakers. Seizure frequency was determined from clinic notes based on parent report at each visit and recorded as average number of seizures per month. Changes to concomitant AEDs and other treatment methods were recorded at each visit as change or no change. Patients who experienced greater than 50% seizure reduction were considered responders.

Data collection and analysis

Study data were collected and imported into REDCap (i.e., Research Electronic Data Capture, Vanderbilt University, Nashville, TN), a secure, web-based application designed to support data capture for research studies. We looked at gender, epilepsy etiology, comorbidities, concomitant AEDs, EEG characteristics, and imaging for potential predictors of response at last follow-up. Additionally, information on the titration schedule of clobazam was analyzed if documented in the patient chart. Starting dose, weeks until first dose increase, target dose, weeks until target dose reached, and dose increase were analyzed as possible predictors of response at last follow-up. We analyzed the relationship between clobazam dose and response at 1, 3, 6, 9, 12 months, and more than 12 months of follow-up. Low doses were considered ≤0.25 mg/kg/day, medium doses were 0.26-0.99 mg/kg/day, and high doses were ≥1.0 mg/kg/day.

SPSS version 21 (SPSS Institute, Chicago, IL) was used for all analyses. Mann-Whitney *U* tests, χ^2 tests, or Fisher exact tests were performed as appropriate, and a Kaplan-Meier survival analysis, including a log rank test, was performed to analyze time until discontinuation with reasons for discontinuation as group factors.

Results

Demographics

Eight-hundred fifteen charts were reviewed. Clobazam was mentioned as a potential therapy in 443 charts, 119 charts had incomplete data, 18 patients did not start clobazam, four patients received clobazam as needed, and two patients discontinued clobazam before 1-month follow-up. Three hundred patients with a median age of 9.1 (range 0.1-31.5) years were included. Demographic data and epilepsy related factors are presented in Tables 1 and 2. Two hundred ninety-two (97.3%) patients were receiving concomitant AEDs: 56 of 300 (18.7%) one additional medication, 106 (35.3%) two additional medications, and 130 (43.3%) three or more additional medications (median 2, interquartile range [IQR] 2-3). The median follow-up duration was 5 months (IQR 3-11 months). In the 3 months before the introduction of clobazam, 132 (44.0%) patients had one seizure type, 110 (36.7%) had two seizure types, 43 (14.3%) had three seizure types, 14 (4.7%) had four seizure types, and one (0.3%) patients had five seizure types. Specific seizure types are reported in Table 1.

Clobazam dose

The median starting dose was 0.2 mg/kg/day (IQR 0.13-0.33), increasing a median of 5 mg/week (IQR 2.5-5) to a median target dose of 0.48 mg/kg/day (IQR 0.26-0.80), with an average dose at last follow up of 0.73 mg/kg/day (SD = 0.53, range 0.05-3.3). There was no association between response and titration schedule (Mann-Whitney *U*-test, not significant [n.s.]). Dose increases during titration (mg/kg/week) were not correlated with seizure reduction.

Overall outcome

Median seizure reduction was 80%. Two-hundred three patients (67.7%) had ≥50% seizure reduction (Table 3), and 84 of 300 (28%) had become seizure-free by the last follow-up. There was no difference between various etiologies (χ^2 test, $P = 0.209$). Follow-up duration was not different in responders and nonresponders (Mann-Whitney *U*-test, $P = 0.777$).