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Clobazam higher-evening differential dosing as an add-on therapy in refractory epilepsy☆

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ABSTRACT

Purpose: Clobazam treatment tailored to the timing of patient's seizures may improve seizure control. We aim to describe the safety and efficacy of higher-evening differential dose of clobazam as add-on therapy in patients with night-time/early morning seizures.
Method: Differential dosing with higher evening dosing was started based on a high proportion of seizures (>80%) at nighttime (6 p.m. to 6 a.m.). Differential dosing was defined as providing more than 50% of the total daily dose of clobazam after 6 p.m.
Results: Twenty-seven patients were treated with clobazam differential dosing as an add-on therapy. The median age was 9.1 years, with 11 (40.7%) females and median of the first follow-up was 2.7 months. Patients with differential dosing tolerated a higher median total clobazam dose of 0.8 mg/kg/d at first follow-up, as compared to 0.6 mg/kg/d in controls. In differential dose, the median percentage of the total clobazam dose administered in the evening was 66.7%. Differential dose patients exhibited a median seizure reduction of 75% as compared to 50% in controls ($p < 0.005$). Patients with generalized seizures benefited the most from differential dosing with a 77.5% median seizure reduction, as compared to 50% in controls ($p = 0.017$).
Conclusion: Higher-evening differential dose of clobazam improved seizure control in patients with predominantly nighttime and early-morning seizures. Chronotherapy tailored to the patients' seizure susceptibility patterns may improve care in epilepsy patients as differential dosing may allow for higher overall treatment doses at times of greatest seizure susceptibility without increased side effects at other times.

1. Introduction

The diurnal and nocturnal pattern of epileptic seizures and influence of the awake and asleep states on seizure presentation have been previously described [1–5]. Chrono-epileptology takes advantage of this knowledge by tailoring antiepileptic drug (AED) schedules on an individual patient basis, providing higher medication doses at the time of greatest seizure susceptibility, without changing the total daily medication dose. Furthermore, the observation of chronotypical patterns in certain types of epilepsy also can provide clues about sleep–awake behavior, and daily patterns of the seizures, as demonstrated in patients with juvenile myoclonic epilepsy who have tendency to wake up later in the morning and go to bed later [6]. Therefore, ultimately a circadian dysrhythmia may facilitate seizures in these patients, and may also help with antiepileptic drug adjustments [6].

Studies including several medications suggest a potential effect of differential dosing. In a pediatric study 17 children with nighttime seizures were treated with differential dosing: this

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study found that 15 (88.2%) patients responded to treatment with ≥50% seizure reduction [7]. Moreover, 11 (73.3%) of these 15 patients became seizure free [7]. Another study in adults with tonic–clonic seizures and previous use of sub-therapeutic doses of phenytoin and carbamazepine found that administration of a higher percentage of the total daily AED dose in the evening improved seizure control and reduced side effects [8]. These studies included different medications including carbamazepine, phenytoin, levetiracetam, oxcarbazepine and valproic acid [7,8]. To date, there is limited data on single medication differential dosing trials, or differential dosing trials with clobazam.

We describe a group of patients with refractory epilepsy who used clobazam as an add-on therapy with differential dosing. The main objective of this study was to describe the safety and efficacy of a higher-evening differential dose of clobazam as an add-on therapy.

2. Methods

2.1. Study design

We performed a retrospective case–control study in patients with refractory epilepsy who started clobazam as an add-on AED at a tertiary pediatric epilepsy center between January 2001 and July 2013. This study was approved by the Institutional Review Board at Boston Children's Hospital.

2.2. Patients

Differential dose patients were defined as patients with a higher proportion of seizures (>80%) at nighttime or early-morning (6 p.m. to 6 a.m.) and who used more than 50% of the total daily dose of clobazam after 6 p.m.

The control group was defined as patients treated with a non-differential dose of clobazam as an add-on antiepileptic medication. Differential dose patients and non-differential dose control patients were matched at a 1:2 proportion by age, etiology, seizure type and, presence or absence of brain lesion on MRI exam.

2.3. Epilepsy classification

Epilepsy syndrome and seizures types were classified according to International League Against Epilepsy (ILAE) 2010 guidelines [9].

2.4. Seizure frequency

Baseline seizure frequency was calculated as average seizure frequency during three months prior to the introduction of clobazam. Patients with more than 50% seizure reduction at the first follow-up visit were classified as responders. Seizure frequency was calculated using all seizure types during the baseline period and during the period up to the first follow-up.

2.5. Data collection

Demographic and seizure data were acquired from clinical charts, and recorded in RedCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN) [10], a standardized web-based data acquisition tool.

2.6. Outcomes

The outcome measure of this study was seizure reduction at first follow-up in patients treated with clobazam differential dosing compared to patients treated with non-differential dosing of clobazam.

2.7. Statistical analysis

Demographic and clinical features of both groups (differential dosing and controls) are summarized in Table 1. Data are presented as median, standard deviation (SD), interquartile range [IQR] (i.e., the 25th percentile to 75th percentile), and percent (%). Dichotomous and categorical data were compared using Chi-square (X^2) test. Normal distribution was tested with Shapiro–Wilk test. For normally distributed data Student's *t*-test was applied and Mann–Whitney *U* test was used for non-normal distributions.

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3. Results

3.1. Demographics

From our cohort of 300 patients treated with clobazam as an add-on therapy, 27 (9%) patients were treated with a differential dose regimen. Median age was 9.1 years (SD: 3.9; IQR: 5.5–10.3). Median time interval of the first follow-up was 2.7 months (SD: 4.4, IQR: 1.3–3.8). Etiologic groups in cases were classified as: genetic in 6 (22.2%), structural/metabolic in 12 (44.5%), and unknown in 9 (33.3%) patients (Table 1).

3.2. Clobazam differential dosing

The median clobazam dose at the first follow-up was 0.8 mg/kg/day (SD: 0.5; IQR: 0.7–1.1 mg/kg/day). The median percentage of the total dose of clobazam administered between 6 p.m. and 6 a.m. was 66.7% (range: 57.1–83.3%). Patients were treated with a median of two concomitant AEDs (IQR: 2–3).

3.3. Outcome of differential dosing patients as compared to non-differential dosing

After adjusting for seizure type, we paired patients with generalized seizures and focal seizures for each medication strategy group. Patients with differential dosing had a five times greater chance of responding to treatment than the control group (Fig. 1), with the following proportions: median seizure reduction of 75% in differential dose patients (IQR: 60–100%) compared to 50% (IQR: 20–83.3%) seizure reduction in controls (OR; 5; [95% CI: 1.5–16.3]; $p < 0.005$, Table 3). Patients with generalized seizures benefitted the most from differential dosing with a 77.5% (IQR: