Epilepsy & Behavior 95 (2019) 161–165

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Clobazam as an adjunctive treatment for infantile spasms

Jongsung Hahn [a], Hyunji Lee [b], Hoon-Chul Kang [b], Joon Soo Lee [b], Heung Dong Kim [b], Se Hee Kim [b,*,1], Min Jung Chang [a,**,1]

[a] Department of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, College of Pharmacy, Yonsei University, Incheon, Republic of Korea
[b] Division of Pediatric Neurology, Department of Pediatrics, Epilepsy Research Institute, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 11 March 2019
Revised 20 March 2019
Accepted 20 March 2019
Available online 4 May 2019

Keywords:
Infantile spasm
Clobazam
Pediatric
Efficacy

ABSTRACT

Infantile spasms constitute a catastrophic epileptic condition. Seizures in approximately half of children with infantile spasms fail to improve with initial treatment attempts; at present, data regarding alternative treatments are limited. We assessed the efficacy of clobazam as an adjunctive therapy in patients whose seizures failed to respond to initial regimens of standard treatment for infantile spasms. All patients from Severance Children's Hospital who received clobazam as adjunctive therapy for infantile spasms were selected for the study. The efficacy of clobazam was evaluated by assessing the daily spasm frequency. Patients were categorized as complete responders if the spasms disappeared within 2 weeks of introducing clobazam, and the patients became spasm-free during weeks 3 and 4. Tolerability was gauged by analyzing adverse events and discontinuation rates. In all, 171 patients qualified for the analysis. Clobazam was introduced after the administration of 2.6 (median; interquartile range [IQR], 1.0–4.0) failed antiepileptic drugs (AEDs), at the age of 8.2 months (IQR, 6.0–10.0 months). After clobazam therapy was initiated, 38 (22.2%) patients became spasm-free for ≥2 weeks. Thirteen out of the 38 complete responders remained spasm-free until the last follow-up and did not require the administration of other AEDs. In 10 patients, the electroencephalogram (EEG) tracings were also within normal limits. These patients were successfully weaned off of all AEDs. Patients with conditions of unknown etiology, who had fewer prior exposures to AEDs, and had not received prior adrenocorticotropic hormone (ACTH)/steroids were more likely to have complete spasm control than the others. Adverse effects were minor, and only 6 of 101 (6%) patients who experienced adverse events had their treatments discontinued during the 3-month follow-up period. The most common adverse events observed were hypersalivation, sedation, and sleep disturbance. Thus, clobazam might be an effective and safe alternative therapeutic option in patients whose seizures failed to respond to initial regimens of standard treatment for infantile spasms. Further prospective studies on clobazam for infantile spasms, focusing on specific good response groups, dosing protocols, and long-term outcome are needed.

© 2019 Elsevier Inc. All rights reserved.

1. Introduction

Infantile spasms constitute an age-specific and catastrophic epileptic condition. In 75–87% of patients with infantile spasms, intellectual impairment occurs, which is aggravated by a failure of achieving spasm control [1,2]. Although standard treatments (i.e., vigabatrin, adrenocorticotropic hormone (ACTH), and steroids) are well established, seizures in 27–62% of patients fail to respond to these medications [3–7]. According to a recent multicenter cohort study, initial treatment failed to control seizures in 59% of children with infantile spasms [3]. However, compelling evidence regarding second-line alternative treatments is still lacking, and choice varies across institutions or clinicians.

Clobazam is the most widely used benzodiazepine for long-term treatment of epilepsy [8]. It is recommended by the National Institute for Health and Care Excellence as an adjunctive treatment for all drug-resistant epileptic disorders [9] and has shown remarkable efficacy for treating seizures of all types [10]. Several studies have shown the efficacy of clobazam in 54–85% of pediatric patients, which was defined as at least 50% reduction in seizure frequency, when clobazam was used as an add-on therapy for refractory epilepsy. Clobazam is specifically effective as an adjunctive therapy in Lennox–Gastaut syndrome, an epilepsy disorder occurring in 20–50% of patients who experienced infantile spasms [11–16]. Recently, a systematic review showed that clobazam

Abbreviations: ACTH, adrenocorticotropic hormone; AEDs, antiepileptic drugs; IRB, institutional review board.

* Corresponding author at: Department of Pediatrics, Yonsei University College of Medicine, Division of Pediatric Neurology, Severance Children's Hospital, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea.
** Corresponding author at: Department of Pharmacy, College of Pharmacy, Yonsei University, 85 Songdogwahak-Ro, Yeonsu-Gu, Incheon 21983, Republic of Korea.
E-mail addresses: SEHEEKIM@yuhs.ac (S.H. Kim), mjchang@yonsei.ac.kr (M.J. Chang).
[1] Contributed equally to this work as corresponding authors.

https://doi.org/10.1016/j.yebeh.2019.03.040
1525-5050/© 2019 Elsevier Inc. All rights reserved.

could be considered as an adjunctive therapy in status epilepticus [17]; continuous infantile spasms have been shown to occur as a unique form of status epilepticus in young infants [18]. Therefore, the potential use of clobazam in patients with infantile spasms needs to be evaluated.

In this study, we assessed the efficacy of clobazam as an adjunctive therapy in patients whose seizures failed to respond to initial regimens of standard treatment for infantile spasms. We also compared baseline characteristics among patients classified by responses and presented drug safety profiles, including the adverse effects and percentage of clobazam discontinuation.

2. Materials and methods

2.1. Patient population

Between September 2005 and September 2015, we performed a retrospective review of the electronic medical records and electroencephalogram (EEG) of patients who were prescribed clobazam as an adjunctive therapy for infantile spasms at the Severance Children's Hospital, a university-affiliated tertiary-care hospital in Seoul, Republic of Korea. This study was approved by the institutional review board (IRB) of Yonsei University (IRB no., 4-2016-0822).

The diagnostic criteria of infantile spasms were as follows: (1) clinical epileptic spasms manifested between 3 months and 2 years of age and (2) characteristic findings on EEG, such as hypsarrhythmia or modified hypsarrhythmia. Only those patients whose seizures failed to respond to treatment with one or more standard antiepileptic drugs (AEDs) for infantile spasms (i.e., vigabatrin, ACTH, and steroids) and who had no alterations in the other AED regimens during 2 weeks of clobazam treatment were included in this study.

Patients with Lennox–Gastaut syndrome, characterized by 1–2 Hz slow, sharp, and wave discharges on EEG; tonic seizures; or delayed seizure onset (>24 months old), were ineligible for this study. Patients with follow-up periods of <3 months, initiation of clobazam after 24 months of age, and EEG abnormalities in the absence of seizures were also excluded.

The following data were retrieved: sex, pediatric and neurological diagnosis, age at the onset of infantile spasms, etiology, follow-up duration, treatment before clobazam, age at the initiation of clobazam, duration of clobazam use, maintenance dose of clobazam, and time to spasm-free state (time from the start of clobazam to the time of becoming spasm-free), and changes in treatment throughout the follow-up period.

2.2. Therapeutic assessment

The efficacy of clobazam was assessed by comparing the daily spasm frequency at weeks 3 and 4 after treatment initiation with that recorded during the 2 weeks just before treatment initiation. The response to clobazam was categorized as complete, partial, or nonresponse. Complete response was defined as the termination of clinical spasms within 2 weeks of clobazam administration and maintenance of the spasm-free status during weeks 3 and 4. Patients who did not completely achieve spasm-free states were categorized as either partial responders, showing 50–99% reduction in spasm frequency during weeks 3 and 4, or nonresponders, showing <50% reduction in spasm frequency or requiring more AEDs (in addition to clobazam) for persistent spasms or abnormal EEG activity. In patients who achieved spasm-free status, data on the resolution of hypsarrhythmia on EEG, recurrence of epileptic spasms, and discontinuation of AEDs were collected. The outcome measures related to drug safety included the number of adverse events and discontinuation of clobazam at months 1 and 3.

2.3. Statistical analysis

Descriptive analyses were performed using the demographic and baseline characteristics of all participants. All variables were individually expressed as numerical values (%), mean ± standard deviation, or median (interquartile range [IQR]). Statistical analysis was performed using SPSS ver. 22 (IBM Corp., Armonk, NY). Fisher's exact test and Mann–Whitney test were used to analyze the differences (at the 95% level of significance) in demographic data, treatment history, and characteristics between patients classified as complete responders and others (partial and nonresponders). Values with $p < 0.05$ were considered statistically significant.

3. Results

3.1. Patient characteristics

In all, 171 patients with infantile spasms were included, with 99 male patients (57.9%). The median age at spasm onset was 6.3 months (IQR, 5.0–8.0 months), and age at clobazam initiation was 8.2 months (IQR, 6.0–10.0 months). Three patients (1.8%) had a history of surgery, and 23 (13.5%) had partaken in ketogenic diets without success. The median number of failed AEDs before clobazam was 2.6 (IQR, 1.0–4.0). The common etiologies of infantile spasms were hypoxic/ischemic encephalopathy (31, 18.1%), malformations of cortical development (27, 15.8%), and metabolic defects (19, 11.1%). The etiologies were unknown in 75 patients (43.9%). The general characteristics of the subjects are listed in Table 1.

3.2. Response to clobazam

After clobazam was started, 103 patients (60.2%) achieved ≥50% reduction in seizure frequency, with 38 (22.2%) complete responders. The remaining 68 patients (39.8%) were nonresponders and experienced <50% seizure reduction. Thirteen out of the 38 complete responders remained spasm-free until the last follow-up and did not require the administration of other AEDs. Among them, 10 patients were successfully weaned off of all AEDs, and remaining 3 patients remained on clobazam because of EEG abnormalities and the potential for occasional spasms triggered by illness or other factors. The median time to spasm-free states was 8 days (IQR, 2–10 days).

Table 1
Clinical characteristics of the study population.

	Number/median (interquartile range) (n = 171)
Sex	
Male	99
Female	72
Age at infantile spasm onset (months)	6.3 (5.0–8.0)
Etiology	
Hypoxic ischemic encephalopathy	31
Malformations of cortical development	27
Metabolic	19
Genetic	8
Cerebrovascular	7
Infectious	2
Tumor	2
Unknown	75
Follow-up duration (months)	50.2 (22.0–71.0)
Treatment before clobazam	
Number of AEDs before clobazam	2.6 (1.0–4.0)
History of ketogenic diet before clobazam	23
History of surgery before clobazam	3
Clobazam use	
Age at clobazam initiation (months)	8.2 (6.0–10.0)
Duration of clobazam use (months)	24.3 (5.3–30.1)
Maintenance dosage of clobazam (mg)	10.2 (7.5–12.5)

Values are the number or median (interquartile range). AEDs, antiepileptic drugs.

Table 2
Baseline characteristics of patients based on the response rate (complete responder vs others).

Clinical parameters	Complete responders (n = 38)	Others (partial or nonresponders) (n = 133)	*p*-Value
Sex			0.456[a]
Male	24 (24.2)	75 (75.8)	
Female	14 (19.4)	58 (80.6)	
Etiology			0.048[a]
Unknown	22 (29.3)	53 (70.7)	
Known	16 (16.1)	80 (83.9)	
Age at spasm onset (months)	6.29 (1.81)	6.35 (2.33)	0.897[b]
Number of prior AEDs	2.24 (1.38)	2.69 (1.50)	0.079[b]
Prior AEDs			0.002[a]
ACTH or steroids	23 (17.8)	106 (82.2)	
Vigabatrin and/or other AEDs	15 (35.7)	27 (64.3)	
Age at clobazam initiation (months)	7.68 (3.78)	8.37 (3.65)	0.129[b]
Time between first AED and clobazam initiation (months)	1.45 (3.18)	2.07 (3.20)	0.078[b]
Duration of clobazam use (months)	23.26 (21.54)	24.61 (29.20)	0.782[b]
Maintenance dose of clobazam (mg/day)	7.90 (3.26)	10.81 (4.42)	<0.001[b]

Values are the mean (standard deviation), except for sex, prior AEDs, and etiology.
[a] Fisher's exact test.
[b] Mann–Whitney test.

3.3. Factors influencing the response to clobazam

Baseline characteristics between patients who were classified as complete responders and those who were partial or nonresponders to clobazam as adjunctive therapy are shown in Table 2. Statistically significant baseline differences in etiology were found among the response groups ($p = 0.048$). Complete responders were likely to have unknown etiology. In comparing patient who had received prior ACTH/steroids with those who had not, patients receiving ACTH/steroids were associated with low complete response rate (35.7% vs 17.8%, $p = 0.002$). The maintenance dose also significantly differed across the response groups, as patients classified as partial or nonresponders received significantly large maintenance dose than complete responders (7.9 ± 3.3 mg vs 10.8 ± 4.4 mg, $p < 0.001$). No statistically significant differences were noted between the groups based on sex, age at spasm onset, number of failed AEDs before clobazam, age at clobazam initiation, time between first AED and clobazam initiation, and duration of clobazam use. In addition, when we compared the 10 patients who were weaned off of all AEDs with nonresponders, the two groups did not differ significantly in terms of sex, age at spasm onset, age at clobazam initiation, duration of clobazam use, time between first AED and clobazam initiation, and duration of clobazam use. However, unlike nonresponders, patients who were successfully weaned off of all AEDs were more likely to have unknown etiology ($p < 0.001$), be on fewer AEDs before clobazam (1.8 ± 0.8 vs 2.9 ± 1.6; $p = 0.047$), and respond to lower maintenance dose (6.0 ± 2.1 mg vs 10.7 ± 4.3 mg, $p = 0.001$; Table 3). The response to clobazam per underlying etiology is shown in Table 4. Infants with a diagnosis of cerebrovascular disease showed the highest complete response rate (42.9%) to clobazam, followed by those with genetic (37.5%) and unknown (29.3%) etiology. The most commonly administered clobazam maintenance dose was 10 mg/day, which was received by 56 patients (32.7%). The maintenance dose of over 17.5 mg/day was only used in 13 patients in whom spasms were not controlled (Table 5).

Table 3
Baseline characteristics of patients on the response rate (patients with all AEDs weaned off vs nonresponders).

Clinical parameters	Patients with all AEDs weaned off (n = 10)	Nonresponders (n = 68)	*p*-Value
Sex (male)	7	39	0.448[a]
Etiology			<0.001[a]
Unknown	10	27	
Known	0	41	
Age at spasm onset (months)	6.30 (1.83)	6.28 (2.38)	0.768[b]
AEDs received before clobazam	1.80 (0.79)	2.90 (1.62)	0.047[b]
Age at clobazam initiation (months)	7.30 (2.21)	8.56 (4.18)	0.494[b]
Duration of clobazam use (months)	10.76 (10.33)	22.15 (26.72)	0.339[b]
Time between first AED and clobazam initiation (months)	0.92 (1.03)	2.28 (3.60)	0.535[b]
Duration of clobazam use (months)	10.76 (10.33)	22.15 (26.72)	0.339[b]
Maintenance dose of clobazam (mg/day)	6.00 (2.11)	10.66 (4.29)	0.001[b]

Values are the mean (standard deviation) unless otherwise indicated.
[a] Fisher's exact test.
[b] Mann–Whitney test.

Table 4
Etiologies of infantile spasms in the clobazam-treated patients.

Etiology	Total (n = 171)	Complete responders (n = 38)	Others (partial or nonresponders) (n = 133)
Hypoxic ischemic encephalopathy	31	5 (16.1)	26 (83.9)
Malformations of cortical development	27	3 (11.1)	24 (88.9)
Metabolic	19	2 (10.5)	17 (89.5)
Genetic	8	3 (37.5)	5 (62.5)
Cerebrovascular	7	3 (42.9)	4 (57.1)
Infectious	2	0 (0.0)	2 (100.0)
Tumor	2	0 (0.0)	2 (100.0)
Unknown	75	22 (29.3)	53 (70.7)

3.4. Adverse events

In all, 101 of 171 patients (59.1%) experienced adverse events, and 57 (33.3%) experienced more than one adverse event (Table 6). The most common adverse events were hypersalivation (39.3%), followed by sedation (26.7%) and sleep disturbance (21.5%). At 1 month, 11 patients (6.4%) had discontinued clobazam because of ineffectiveness (9), adverse events (3), or both (1); at 3 months, 20 patients (11.7%) had discontinued clobazam because of ineffectiveness (18), adverse events (6), or both (4). The most common reasons for the discontinuation of clobazam were ineffectiveness and adverse event of irritability.

4. Discussion

This retrospective study, which, to our knowledge, is the first large study focusing on clobazam in the narrower context of alternative treatment for infantile spasms, showed that clobazam was effective in ceasing spasms. In 22.2% of our patients whose seizures failed to respond to standard AED treatment, clobazam use caused the cessation of spasms; further, 7.6% of clobazam recipients achieved long-term spasm relief, EEG normalization, and were weaned off of all AEDs. These findings indicate that clobazam could be a potential option for

Table 5
Distribution of the clobazam-treated patients by maintenance dose required for spasm control.

Dose (mg/day)	Complete responders (n = 38)	Others (partial or nonresponders) (n = 133)
2.5	1	1
5.0	15	21
7.5	7	20
10.0	10	46
12.5	2	7
15.0	3	25
17.5	0	3
≥20.0	0	10

Table 6
Adverse events.

Adverse event	Frequency (percent, %)	Discontinuation within 1 month	Discontinuation within 3 months
Hypersalivation	53 (39.3)	–	–
Sedation	36 (26.7)	1	2
Sleep disturbance	29 (21.5)	–	–
Gastrointestinal problems	11 (8.1)	1	1
Irritability	6 (4.4)	1	3

Reasons for discontinuation	Discontinuation within 1 month	Discontinuation within 3 months
Ineffective	9	18
Adverse events	3	6
Ineffective + adverse events	1	4

the management of infantile spasms in patients whose seizures fail to respond to standard AEDs. Although clobazam is a well-known AED commonly used for drug-resistant epilepsies, data on its utility in instances of infantile spasms are very limited. To date, only a few studies with small numbers of patients with infantile spasms have assessed clobazam use for drug-resistant epilepsies [1,13,14]. However, their findings clearly support its efficacy in treating infantile spasms and drug-resistant epilepsies in general [19,20]. The efficacy of clobazam for infantile spasms can be explained in part by its high efficacy in the setting of Lennox–Gastaut syndrome, which frequently evolves from infantile spasms. In both conditions, seizures are characterized as spasms or brief tonic/atonic head drops that are associated with severely abnormal ictal EEGs (marked by electrodecrements) and developmental regression. Given their shared characteristics, similar responses to treatment would be expected. Several other AEDs as second-line therapy for infantile spasms have been investigated, such as topiramate [21,22], zonisamide [23], felbamate [24], valproic acid [25], and nitrazepam [26], but all in very limited number of infants and reports of efficacy. Comparing these studies is difficult because the definition of response and outcome measure differed across the studies.

In the present study, clobazam-treated patients with unknown etiology, did not receive prior ACTH/steroids, and few prior exposures to AEDs were found to be more likely to have a complete spasm control. These data suggest that controlling spasms might be more difficult in patients with known etiology than in those with unknown etiology. When the response rate per etiology was explored, we found that patients with cerebrovascular and genetic etiology had better chances of achieving complete response than the others. However, because of the small number of patients in each etiology (genetic, 8; cerebrovascular, 7), determining the particular type of etiology for which clobazam was more useful is difficult. Interestingly, patients who had received prior ACTH/steroids showed lower response rate to clobazam than those who had not received. This finding suggests that patients whose seizures failed to improve with ACTH/steroids might have severe drug-resistant spasms, which led to failure of clobazam. Complete spasm control in patients with less usage of AEDs before clobazam treatment implies that initiating appropriate treatment early was important. These findings are consistent with those of previous studies advocating that cryptogenic etiology and early treatment initiation are predictive factors of good therapeutic outcomes in patients with infantile spasms [27]. Taken together, these findings emphasize the importance of identifying this distinct patient subset, and thus controlling spasms and promoting better neurodevelopment.

The clobazam dosing recommended by the Food and Drug Administration was only established in patients with Lennox–Gastaut syndrome who were more than 2 years old. It is based on the total daily dose as follows: patients ≤30 kg should initiate 5 mg/day and titrate weekly as tolerated up to 20 mg/day and patients >30 kg should initiate 10 mg/day and titrate weekly as tolerated up to 40 mg/day [28]. Notably, seizures of most of our patients responded well to maintenance dose of 7.9 ± 3.26 mg/day. We observed higher response rates in patients receiving lower maintenance doses of clobazam. This result might imply that increasing the dose of clobazam in patients who do not respond to clobazam would not be useful and could only lead to adverse events.

In our study, a high percentage of patients (59.1%) experienced side effects during clobazam treatment, but most (95/101, 94%) continued its use during the 3-month follow-up. The most common side effects included hypersalivation, sedation, and sleep disturbance. Because clobazam is a 1,5-benzodiazepine, lesser sedation and fewer effects on psychomotor impairment would be expected than when other conventional 1,4-benzodiazepines are used [29]. The long-term efficacy and safety of clobazam therapy have already been established in other epilepsy syndromes such as Lennox–Gastaut syndrome. In our study, the median duration of clobazam use was 24.3 months; therefore, clobazam is apparently both effective and tolerable in the treatment of infantile spasms.

As a retrospective study, our findings have a few limitations. First, variability in previously unsuccessful treatment attempts and concurrent administration of prior AEDs could be major confounding factors, as the cumulative or delayed effect of previously administered AEDs cannot be excluded. In addition, the timing of clobazam administration, maintenance dose of clobazam, and clobazam exposure time varied in the study population. These could be considered as an added confounder to clobazam efficacy. Second, this study lacks analysis on relapses and long-term outcome because each patient had a different follow-up duration. However, we believe that our findings reflect the relative prolongation of follow-up time, which enabled the description of clobazam treatment-related clinical settings, including adverse events. Despite the retrospective character, this study could be useful for clinicians who treat infantile spasms with clobazam. Large prospective studies are needed to determine the long-term efficacy and safety as well as the early clobazam efficacy as adjunctive therapy in the management of infantile spasms.

5. Conclusion

Although the current evidence is limited, short-term efficacy and tolerance of clobazam suggest that it is a potential alternative therapeutic option for infantile spasms. Further prospective studies on clobazam for infantile spasms focusing on specific good response group, dosing protocols, and long-term outcomes are needed.

Acknowledgments

None.

Conflict of interest

None.

Funding

This work was supported by a faculty research grant from the Yonsei University College of Medicine [grant number 6-2018-0057] and Graduate School of YONSEI University Research Scholarship Grants in 2017.

References

[1] Lagae L, Verhelst H, Ceulemans B, De Meirleir L, Nassogne MC, De Borchgrave V, et al. Treatment and long term outcome in West syndrome: the clinical reality. A multicentre follow up study. Seizure 2010;19:159–64.
[2] Lee J, Lee JH, Yu HJ, Lee M. Prognostic factors of infantile spasms: role of treatment options including a ketogenic diet. Brain Dev 2013;35:821–6.
[3] Knupp KG, Leister E, Coryell J, Nickels KC, Ryan N, Juarez-Colunga E, et al. Response to second treatment after initial failed treatment in a multicenter prospective infantile spasms cohort. Epilepsia 2016;57:1834–42.

[4] Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. Lancet 2004;364:1773–8.
[5] Appleton RE, Peters AC, Mumford JP, Shaw DE. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. Epilepsia 1999;40:1627–33.
[6] Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. Epilepsia 1997;38:1270–4.
[7] Knupp KG, Coryell J, Nickels KC, Ryan N, Leister E, Loddenkemper T, et al. Response to treatment in a prospective national infantile spasms cohort. Ann Neurol 2016;79:475–84.
[8] Shorvon SD. The use of clobazam, midazolam, and nitrazepam in epilepsy. Epilepsia 1998;39:S15–23.
[9] National Clinical Guideline C. National Institute for Health and Clinical Excellence: Guidance. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care: pharmacological update of clinical guideline 20. London: Royal College of Physicians (UK) National Clinical Guideline Centre; 2012.
[10] Cramer JA, Sapin C, Francois C. Indirect comparison of clobazam and other therapies for Lennox–Gastaut syndrome. Acta Neurol Scand 2013;128:91–9.
[11] Ng Y-T, Conry J, Mitchell WG, Buchhalter J, Isojarvi J, Lee D, et al. Clobazam is equally safe and efficacious for seizures associated with Lennox–Gastaut syndrome across different age groups: post hoc analyses of short- and long-term clinical trial results. Behavior;Epilepsy Behav 2015;46:221–6.
[12] Conry JA, Ng YT, Paolicchi JM, Kernitsky L, Mitchell WG, Ritter FJ, et al. Clobazam in the treatment of Lennox–Gastaut syndrome. Epilepsia 2009;50:1158–66.
[13] Trevathan E, Murphy CC, Yeargin-Allsopp M. The descriptive epidemiology of infantile spasms among Atlanta children. Epilepsia 1999;40:748–51.
[14] Rantala H, Putkonen T. Occurrence, outcome, and prognostic factors of infantile spasms and Lennox–Gastaut syndrome. Epilepsia 1999;40:286–9.
[15] Weinmann H-M. Lennox–Gastaut syndrome and its relationship to infantile spasms (West's syndrome). The Lennox–Gastaut syndrome: neurology und neurobiology, 45. 1988. p. 310–6.
[16] Lombroso CT. A prospective study of infantile spasms: clinical and therapeutic correlations. Epilepsia 1983;24:135–58.
[17] Mahmoud SH, Rans C. Systematic review of clobazam use in patients with status epilepticus. Epilepsia Open 2018;3:323–30.
[18] Coulter DL. Continuous infantile spasms as a form of status epilepticus. J Child Neurol 1986;1:215–7.
[19] Perry MS, Bailey L, Malik S, Gilson C, Kotecha A, Hernandez A. Clobazam for the treatment of intractable epilepsy in children. J Child Neurol 2013;28:34–9.
[20] Sheth RD, Ronen GM, Goulden KJ, Penney S, Bodensteiner JB. Clobazam for intractable pediatric epilepsy. J Child Neurol 1995;10:205–8.
[21] Weber A, Cole JW, Mytinger JR. Infantile spasms respond poorly to topiramate. Pediatr Neurol 2015;53:130–4.
[22] Mahmoud AA, Rizk TM, Mansy AA, Ali JA, Al-Tannir MA. Ineffectiveness of topiramate and levetiracetam in infantile spasms non-responsive to steroids. Open labeled randomized prospective study. Neurosciences (Riyadh) 2013;18:143–6.
[23] Yum MS, Ko TS. Zonisamide in West syndrome: an open label study. Epileptic Disord 2009;11:339–44.
[24] Hosain S, Nagarajan L, Carson D, Solomon G, Mast J, Labar D. Felbamate for refractory infantile spasms. J Child Neurol 1997;12:466–8.
[25] Chandra S, Bhave A, Bhargava R, Kumar C, Kumar R. West syndrome: response to valproate. Front Neurol 2012;3:166.
[26] Fallah R, Salor F, Akhavan Karbasi S, Motaghipisheh H. Randomised clinical efficacy trial of topiramate and nitrazepam in treatment of infantile spasms. Iran J Child Neurol 2014;8:12–9.
[27] Cohen-Sadan S, Kramer U, Ben-Zeev B, Lahat E, Sahar E, Nevo Y, et al. Multicenter long-term follow-up of children with idiopathic West syndrome: ACTH versus vigabatrin. Eur J Neurol 2009;16:482–7.
[28] ONFI® (clobazam). Full prescribing information. Deerfield, IL: Lundbeck; 2016.
[29] Wheless JW, Phelps SJ. Clobazam: a newly approved but well-established drug for the treatment of intractable epilepsy syndromes. J Child Neurol 2013;28:219–29.