Am J Clin Exp Immunol 2020;9(4):58-63
www.ajcei.us /ISSN:2164-7712/AJCEI0105901

Original Article

Comparison of the efficacy of Tegatard and Tegretol as a monotherapy in patients with focal seizure with or without secondary generalization

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Received December 4, 2019; Accepted December 22, 2019; Epub October 15, 2020; Published October 30, 2020

Abstract: Background: Carbamazepine is a first line treatment for focal epilepsy. Tegretol and Tegatard are two trade name of Carbamazepine. Tegretol is produced by Novartis Pharmaceutical Company, Switzerland. Recently, Raha pharmaceutical Company in Iran has produced CBZ which trade named is Tegatard. Extended usage of Tegatard instead of Tegretol has economic benefits for Iranian families. In this clinical trial, we aimed to compare therapeutic efficacy and safety of Tegretol and Tegatard in patients suffering from focal seizures with or without secondary generalization. Methods: 200 patients with provoked or non-provoked focal seizure with or without secondary generalization were screened and 180 patients were fulfilled the criteria to enter this double blinded clinical trial study. Patients were divided into two groups, the first group (A) received Tegretol and the second group (B) Tegatard. Carbamazepine (CBZ) was prescribed with doses 10-20 mg/kg every 12 hours by neurologists. The patients were visited after 1, 3 and 6 months and the side effects and lab data in patients were investigated. Results: Patients were divided into two groups, 88 patients in group A (Tegretol) (50 males and 38 females) and 92 in group B (Tegatard) (51 males and 41 females). Mean age of patients was 35.39±11.17 years. There was no significant difference according to age and gender, Carbamazepine dosage, EEG recording, neuroimaging change and adverse effects of antiepileptic drug between two groups (P>0.05). Regarding the drug efficacy, in group A and B, 60 (68%) and 58 (63%) patients were seizure free after 6 month follow up; respectively. The differences between two groups were not statistically significant (*P* value =0.46). Conclusion: Tegatard is an effective drug with similar efficacy, similar side effects and cost-effectiveness compared with Tegretol and could be used widely when indicated.

Keywords: Carbamazepine, tegatard, tegretol, efficacy, side effect, focal seizure

Introduction

Seizure is defined as unpredicted and abnormal brain impulses and epilepsy is the frequent occurrence of seizures [1, 2]. Epilepsy is a common and chronic disease of central nervous system (CNS) which affects millions of people worldwide and brings a heavy socioeconomic burden upon different societies. Furthermore, it has been reported that the prevalence of epilepsy is higher in developing countries [3]. Studies indicate that the chance of at least one seizure episode in lifelong is 9% and the chance of epilepsy is 3% while the prevalence of active epilepsy is only 0.8% [4, 5]. There are different known Predisposing factors for developing epilepsy include: fever, CNS infections, head traumas, CNS structural abnormalities, brain tumors and positive familial history [6]. The most important aspect of epilepsy management is treatments with antiepileptic drugs (AEDs). Studies indicate that seizures are controlled with drug usage in almost 70% of patients with epilepsy and in 20-25% of them; number and severity of seizure attacks are reduced [7, 8]. Phenytoin, carbamazepine (CBZ) and sodium valproate are known as the first line treatments for focal seizure, with beneficial effects on generalized epilepsy [9-12].

CBZ is an oral AEDs agent with slow absorption and has a half-life of 10 to 20 hours. It is also a

strong liver enzyme inducer and as a result, when divided into multiple doses, its half-time decreases to 4 to 12 hours [13]. The mechanism of action of CBZ is by stabilizing the inactive phase of sodium channels and it is also GABA receptor agonist. As mentioned above, CBZ is a first line treatment for focal seizure with mild to moderate side effects [14, 15]. Such side effects occur at the beginning of treatments and are consisted of dizziness, nausea, vomiting, ataxia, diplopia, drowsiness and headache. Serious rare side effects are hematological and hepatic problems [16]. Treatments with CBZ is a long-term treatment for most of the patients and this issue brings a heavy burden for most Iranian families. Tegretol is a trade name of CBZ produced by Novartis Pharmaceutical Company, Switzerland which has proven its efficacy in different studies [17, 18]. Recently, Raha pharmaceutical Company in Iran has produced CBZ which trade named is Tegatard. Extended usage of Tegatard instead of Tegretol has many social and economic benefits and might decrease financial problems for Iranian families. In this clinical trial, we aimed to compare the therapeutic efficacy and safety of Tegretol and Tegatard in patients suffering from focal seizure.

Methods

This double-blinded randomized clinical trial was performed between October 2016 and September 2017 in Isfahan, Iran. Our study populations were patients who were formerly diagnosed with epilepsy, referred to neurology clinics or epilepsy centers in Isfahan. Patients of ages above 18 with provoked or non-provoked focal seizure with or without secondary generalization were enrolled in this study. Exclusion criteria were: 1) patients unwilling to continue the study 2) patients requires polytherapy for controlling the seizure 3) patients change the drug during follow up 4) patients suffered from severe drug adverse effects. It should also be noted that all the patients and healthy control group signed the written informed consent, and also the Ethical Committee on Human Research of Isfahan University of Medical Sciences (IR.MUI.REC.1395.3.708) and Iranian Registry of Clinical Trials (IRCT2017092114217N1) approved this study. A total number of 200 patients were screened for this study, out of them, in 8 patients under treatment with Tagretol, the drug changed to Tegatard and then were excluded of the study, 12 patients were under 18 years and excluded from study, thus, 180 were fulfilled the criteria to enter the study analysis. Demographics and seizure features including the type of seizure, seizure free duration, Electroencephalography (EEG) findings and adverse effect of drug were collected and surveyed by expert neurologists. Neuroimaging (Magnetic resonance imaging (MRI) and Computed tomography scan (CT-scan)) were also performed for each patient.

This patient population was randomized by a computer-generated list in two groups; regarding the treatment. The first group (group A; N=88) received Tegretol as an AED, and the other group (group B; N=92) treated with Tegatard. CBZ was prescribed with doses 10-20 mg/kg every 12 hours by neurologists. Complete blood count (CBC) and liver function tests (LFT) were checked at the beginning of the study, after one, three and six month. They have visited after one, three and six month, and drug side effect, seizure recurrence, neurological complications such as dizziness, vertigo, blurred vision, gait imbalance and etc. were asked.

Statistics

The data were analyzed with SPSS version 24, Quantitative data were presented as mean and standard deviation, and qualitative data were presented as frequency or percentage. Independent t-test and Chi-Square were used to analyze data. $P<0.05$ was considered significant.

Results

Patients characteristic and demographics

180 Patients were divided into two groups, 88 patients in group A (Tegretol) (50 males and 38 females) and 92 patients in group B (Tegatard) (51 males and 41 females). Mean age of patients was 35.39±11.17 years (34.69 and 36.06 years in group A and B; respectively; range: 18-71 years). There was no significant difference according to age and gender between the two groups ($P>0.05$). 137 cases had abnormal EEGs, 17 cases had abnormal CTs, and 19 cases had abnormal MRIs. There was no significant difference between the two

Table 1. Overall characteristics of patients

Variables		Tegretol	Tegatard	Total	*P*-value
Age (years)		34.69±11.25	36.06±11.11	35.39±11.17	0.41
Gender	Female	50	51	101	0.48
	Male	38	41	79	
Dosage (mg)		580.48±214.55	583.52±193.24	582.03±203.37	0.92
Abnormal EEG		70 (79%)	77 (72%)	137 (76.1%)	0.19
Abnormal CT		7 (8%)	10 (10.8%)	17 (9.4%)	0.34
Abnormal MRI		6 (6.8%)	13 (14%)	19 (10.5%)	0.08
Seizure freedom at the end of 6 month		60 (68%)	58 (63%)	118 (65%)	0.28

Table 2. Predisposing factors of patients in both groups

Predisposing factors	Tegretol	Tegatard	Total	*P*-value
Positive family history	36 (40.9%)	30 (32%)	69 (36.6%)	0.16
Head trauma	5 (5.6%)	11 (11.9%)	16 (8.8%)	0.11
Stroke	4 (4.5%)	0	4 (2.2%)	0.055
Dementia	0	1 (1%)	1 (0.5%)	0.51
Febrile seizure	13 (14.7%)	18 (19.5%)	31 (17.2%)	0.25
Development disorder	2 (2.2%)	0	2 (1.1%)	0.23

groups regarding CBZ dosage, EEG changes and Neuro imaging findings (P>0.05) (**Table 1**).

Treatment efficacy

118 patients (65%) were seizure free after 6 month follow up; 60 (68%) in group A and 58 (63%) patients in group B. The differences between two group were not statistically significant (*P*-value =0.46) (**Table 1**).

Predisposing factors

Predisposing factors of patients were included positive family history (36.6%), head trauma (8.8%), stroke (2.2%), dementia (0.5%), seizure in childhood (17.2%) and development disorder (1.1%). There was no significant difference between groups based on positive family history, head trauma, stroke, dementia, seizure in childhood, and development disorder (P>0.05) (**Table 2**).

Drug adverse effect

Adverse effect of study were included headache (15%), dizziness (7.2%), agitation (6.1%), weight gain (5.5%), insomnia (5.5%), anorexia (5%), nausea (5%), fatigue (4.4%), drowsiness (4.4%), hypotension (4.4%), fear (3.8%), itching (3.8%), diplopia (2.7%), anxiety (3.3%), delusion (2.7%), depression (2.2%), tremor (2.2%), skin rash (1.6%), epistaxis (1.6%), impairment (1.1%), chorea athetosis (1.1%), flushing (0.5%), hearing numbness (0.5%), Mild to moderate leucopenia (8.3%) and rise LFT (7.2%). There was no statistically significant difference between two groups based on drug complications (P>0.05) (**Table 3**). Comparison of the Number of patients with no side effect between two groups was not statistically significant (41 (46%) patients in group A and 37 (40%) in group B; *P* value =0.23).

Discussion

AEDs are aimed to achieve seizure freedom with minimally adverse effects. Numerous AEDs are licensed as monotherapy for focal seizure in Adults. CBZ is one of these drugs.

In this study Efficacy of Tegatard and Tegretol were compared by assessing the seizure freedom after 6 month. 118 patients (65%) were seizure free after 6 month follow up; 60 (68%) in group A and 58 (63%) patients in group B. The differences between two group were not statistically significant (*P*-value =0.46). In a study performed by Swaroop et al. 71.4% of patients on CBZ were seizure free after 6 month [19]. In another studies aimed to compare Levetiracetam efficacy versus CBZ, The seizure freedom rate at the end of 6 months was 65% in Perry et al study [20], 62% in KOMET trial [21] and 72.8% in Brodie et al study [22].

There have also been some reported side effects associated with CBZ. These side effects include: Cutaneous adverse effects, vertigo, chorea athetosis, depression, insomnia, drows-

Table 3. Complications of drugs after medication in the groups

Complication		Tegretol	Tegatard	Total	*P*-value
Nausea		4 (3.4%)	5 (4.3%)	9 (5%)	0.52
Tremor		2 (2.2%)	2 (2.1%)	4 (2.2%)	0.67
Diplopia		2 (2.2%)	3 (3.2%)	5 (2.7%)	0.52
Hypotension		4 (4.5%)	4 (5.4%)	8 (4.4%)	0.61
Insomnia		4 (4.5%)	6 (6.5%)	10 (5.5%)	0.40
Agitation		6 (6.8%)	5 (5.4%)	11 (6.1%)	0.47
Drowsiness		3 (3.4%)	5 (5.4%)	8 (4.4%)	0.38
Fear		4 (4.5%)	3 (3.2%)	7 (3.8%)	0.47
Weight Gain		4 (4.5%)	6 (6.5%)	10 (5.5%)	0.40
Epistaxis		1 (1.1%)	2 (2.1%)	3 (1.6%)	0.51
Headache		14 (15.9%)	13 (14.1%)	29 (15%)	0.45
Dizziness		7 (7.9%)	6 (7.6%)	13 (7.2%)	0.46
Anorexia		3 (3.4%)	6 (6.5%)	9 (5%)	0.27
chorea Athetosis		2 (2.2%)	0	2 (1.1%)	0.23
Depression		2 (2.2%)	2 (2.1%)	4 (2.2%)	0.67
Anxiety		2 (2.2%)	4 (4.3%)	6 (3.3%)	0.36
Delusion		3 (3.4%)	2 (2.1%)	5 (2.7%)	0.48
Flushing		0	1 (1%)	1 (0.5%)	0.51
Hearing impairment		0	2 (2.1%)	2 (1.1%)	0.26
Numbness		0	1 (1%)	1 (0.5%)	0.51
Fatigue		4 (4.5%)	4 (5.4%)	8 (4.4%)	0.61
Skin rash		1 (1.1%)	2 (2.1%)	3 (1.6%)	0.51
Itching		2 (2.2%)	5(5.4%)	7 (3.8%)	0.24
Lab data	Leucopenia	7 (7.9%)	8 (8.6)	15 (8.3%)	0.44
	Rise LFT	5 (5.5%)	8 (8.6%)	13 (7.2%)	0.31

iness, poor coordination, hypotension, and diplopia [23, 24]. Drug adverse effects of our patients are summarized in **Table 3**. Here in this article we compared two types of CBZ and had a survey on their possible side effects. We indicated that there is no statistically significant difference between Tegretol and Tegatard regarding their side effects. Adverse effects of CBZ were discussed in different studies each pretending a different rate for adverse effects [16, 25, 26]. This issue could be related to drug characteristics and also different races among patients. Plumpton and colleagues had reported that some adverse effects of CBZ such as cutaneous side effects might be correlated to special HLAs and HLA-A*31:01 was introduced as a predictor factor [27]. For example, K. Zeng et al [16] reported these side effect of CBZ between 168 patients among Chinese population: loss of appetite (3%), nausea (4.8%), Fatigue and tiredness (4.2%), dizziness (1.2%), memory problem (2.4%), Somnolence (3%), Insomnia (1.8%), rash (1.2%) and Leucopenia (3%); K. Zeng et al reported no case of Tremor, Nystagmus, and Liver damage as a side effect of CBZ. Different trials have had surveys on different kinds of CBZ as an AED to prove their efficacy and compare their side effects. We also indicated that both Tegretol and Tegatard, had positive effects. All these studies seek for the best methods and kinds of CBZ with the lowest side effects.

Studies emphasize the cost-effectiveness of drugs and declare that economic aspects of medications as well as any other therapeutic procedure must be noted [28]. Owens and colleagues declare that costs, harms, and benefits of medical interventions are one of the most important principles and the best drug with the least costs and harms must be selected [29] and this principle must be considered in order to choose the best cost-effective drugs. Here in this study, we indicated that both Tegretol and Tegatard have same efficacy and same adverse effects. As described above, Tegatard is CBZ produced by Raha pharmaceutical Company in Iran. The prices comparison between Tegretol and Tegatard could indicate a difference and Tegretol is more expensive than Tegatard. So, patients might show poor compliance due to economic issues, as in our studies 8 patients were changing their medication from Tegretol to Tegatard due to financial problems. The similarity in drug effects and side effects of Tegatard compared to Tegretol indicates that Tegatard has the potential to be a suitable replacement of Tegretol and due to economic issues; it could also be a cost-effective choice for patients.

Conclusion

Our study showed that Tegatard is effective drugs to treat focal seizure with no significant differences in efficacy and side effects versus

Tegretol. On the other hand the price of Tegretol is more expensive than Tegatard. Thus, due to similar efficacy and adverse effects and considerable less price of Tegatard it could be used widely when indicated.

Disclosure of conflict of interest

None.

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References

[1] Engel J. Seizures and epilepsy: Oxford University Press 2013.
[2] Mehvari J, Zare M, Andami R, Ghadimi K and Tabrizi N. Ictal and interictal electroencephalography of mesial and lateral temporal lobe epilepsy; a comparative study. Caspian J Neurol Sci 2017; 3: 222-30.
[3] Bell GS, Neligan A and Sander JW. An unknown quantity-the worldwide prevalence of epilepsy. Epilepsia 2014; 55: 958-62.
[4] Pellock JM. Overview: definitions and classifications of seizure emergencies. J Child Neurol 2007; 22 Suppl: S9-S13.
[5] Italiano D, Ferlazzo E, Gasparini S, Spina E, Mondello S, Labate A, Gambardella A and Aguglia U. Generalized versus partial reflex seizures: a review. Seizure 2014; 23: 512-20.
[6] Ngugi AK, Bottomley C, Kleinschmidt I, Wagner RG, Kakooza-Mwesige A, Ae-Ngibise K, Owusu-Agyei S, Masanja H, Kamuyu G, Odhiambo R, Chengo E, Sander JW and Newton CR; SEEDS group. Prevalence of active convulsive epilepsy in sub-Saharan Africa and associated risk factors: cross-sectional and case-control studies. Seizure 2014; 23: 512-20.
[7] Ebrahimi H and Asadi M. Effect of charged amino acids on convulsion due to penthylentetrazol in male adult rat. Iran J Neurol 2005; 4: 13-7.
[8] Brodie M, Barry S, Bamagous G, Norrie J and Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012; 78: 1548-54.
[9] Sorensen AT and Kokaia M. Novel approaches to epilepsy treatment. Epilepsia 2013; 54: 1-10.
[10] Bialer M. Chemical properties of antiepileptic drugs (AEDs). Adv Drug Deliv Rev 2012; 64: 887-95.
[11] Rafiee Zadeh A, Askari M, Azadani NN, Ataei A, Ghadimi K, Tavoosi N and Falahatian M. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 1. Int J Physiol Pathophysiol Pharmacol 2019; 11: 95-104.
[12] Rafiee Zadeh A, Ghadimi K, Ataei A, Askari M, Sheikhinia N, Tavoosi N and Falahatian M. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 2. Int J Physiol Pathophysiol Pharmacol 2019; 11: 105.
[13] Tolou-Ghamari Z, Zare M, Habibabadi JM and Najafi MR. A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012. J Res Med Sci 2013; 18 Suppl 1: S81-5.
[14] Sørensen AT and Kokaia M. Novel approaches to epilepsy treatment. Epilepsia 2013; 54: 1-10.
[15] Bialer M. Chemical properties of antiepileptic drugs (AEDs). Adv Drug Deliv Rev 2012; 64: 887-95.
[16] Zeng K, Wang X, Xi Z and Yan Y. Adverse effects of carbamazepine, phenytoin, valproate and lamotrigine monotherapy in epileptic adult Chinese patients. Clin Neurol Neurosurg 2010; 112: 291-5.
[17] Desmarais JE, Beauclair L and Margolese HC. Switching from brand-name to generic psychotropic medications: a literature review. CNS Neurosci Ther 2011; 17: 750-60.
[18] Chouchi M, Kaabachi W, Tizaoui K, Daghfous R, Aidli S and Hila L. The HLA-B* 15: 02 polymorphism and tegretol®-induced serious cutaneous reactions in epilepsy: an updated systematic review and meta-analysis. Rev Neurol (Paris) 2018; 174: 278-91.
[19] Suresh SH, Chakraborty A, Virupakshaiah A and Kumar N. Efficacy and safety of levetiracetam and carbamazepine as monotherapy in partial seizures. Epilepsy Res Treat 2015; 2015: 415082.
[20] Perry S, Holt P and Benatar M. Levetiracetam versus carbamazepine monotherapy for partial epilepsy in children less than 16 years of age. J Child Neurol 2008; 23: 515-9.
[21] Trinka E, Marson AG, Van Paesschen W, Kälviäinen R, Marovac J, Duncan B, Buyle S, Hallström Y, Hon P, Muscas GC, Newton M, Meencke HJ, Smith PE and Pohlmann-Eden B; KOMET Study Group. KOMET: an unblinded, randomised, two parallel-group, stratified trial comparing the effectiveness of levetiracetam with controlled-release carbamazepine and extended-release sodium valproate as monotherapy in patients with newly diagnosed epilepsy. J Neurol Neurosurg Psychiatry 2013; 84: 1138-47.
[22] Brodie M, Perucca E, Ryvlin P, Ben-Menachem E and Meencke HJ. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology 2007; 68: 402-8.

[23] Powell G, Saunders M, Rigby A and Marson AG. Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy. Cochrane Database Syst Rev 2016; 12: CD007124.
[24] Jung DE, Yu R, Yoon JR, Eun BL, Kwon SH, Lee YJ, Eun SH, Lee JS, Kim HD, Nam SO, Kim GH, Hwang SK, Eom S, Kang DR and Kang HC. Neuropsychological effects of levetiracetam and carbamazepine in children with focal epilepsy. Neurology 2015; 84: 2312-9.
[25] Koliqi R, Polidori C and Islami H. Prevalence of side effects treatment with carbamazepine and other antiepileptics in patients with epilepsy. Mater Sociomed 2015; 27: 167.
[26] Perucca P and Gilliam FG. Adverse effects of antiepileptic drugs. Lancet Neurol 2012; 11: 792-802.
[27] Plumpton CO, Yip VL, Alfirevic A, Marson AG, Pirmohamed M and Hughes DA. Cost-effectiveness of screening for HLA-A* 31: 01 prior to initiation of carbamazepine in epilepsy. Epilepsia 2015; 56: 556-63.
[28] Clement FM, Harris A, Li JJ, Yong K, Lee KM and Manns BJ. Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada. JAMA 2009; 302: 1437-43.
[29] Owens DK, Qaseem A, Chou R and Shekelle P. High-value, cost-conscious health care: concepts for clinicians to evaluate the benefits, harms, and costs of medical interventions. Ann Intern Med 2011; 154: 174-80.