

Full Length Research Paper

Clinical presentation and the efficacy of antiepileptic therapy in the patients with partial and generalized epilepsy

Refah Sayin^{1*}, Temel Tombul¹, Omer Anlar² and Hüseyin Caksen³

¹Department of Neurology, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey.

²Department of Neurology, Ataturk Education and Research Hospital, Ankara, Turkey.

³Department of Pediatrics, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey.

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Epilepsy is an abnormal recurrent disease, resulting from various disorders of central nervous system. In this study, we aimed to compare the patients in terms of therapeutic efficiency. We enrolled a total of 106 patients in the study and of them, 45 were male and 61 were female, aged between 2 to 52 years. Of these patients, 69 (65%) had partial and 37 (35%) had generalized seizures. Seventy three patients were being treated with monotherapy and 33 patients were being treated with polytherapy. The number of the patients that were taking monotherapy was higher in the pediatric group (age, 0 to 16) compared to adult group (age, above 16). In the study, we tried to express the importance of monotherapy in the pediatric patients, the higher number of the pathologies that can be detected using an imaging method in the patients with partial epilepsy compared to that of generalized epilepsy, and the most frequent occurrence of therapeutic resistance in the partial epilepsies.

Key words: Antiepileptic drug, epilepsy, generalized epilepsy, partial epilepsy, treatment.

INTRODUCTION

Epilepsy is a common condition characterized by recurrent seizures. As the underlying pathophysiologic mechanisms of the epilepsy are still unknown, the therapeutic approaches are only consisted of the inhibition of epileptic seizures using the existing antiepileptic drugs (AEDs) (Najm et al., 2001). The majority of the diseases seen in the community results from a complex etiology that includes the interaction between one or more genes and environmental factors (Bate and Gardiner, 1999). It is thought that the etiology of at least 40% of the epileptic cases is due to genetic factors (Berkovic and Scheffer, 1999). While, in the children of the parents with idiopathic generalized epilepsy, the risk for epilepsy is increased, the risk for epilepsy in a child of the parents with idiopathic absence

seizures is reported to be about 9% (Shorvon 1995; Elmslie and Gardiner, 1997). For the epilepsy, the diagnosis maybe based on episodic diagnosis, syndrome-based diagnosis and etiological diagnosis. The goals of the antiepileptic therapy are to provide a complete control of the seizures without or with the least side effects and to ensure the normal life style. To choose the most suitable AED for individual patients, it is necessary to have a detailed knowledge about the properties of the patients and of the existing AEDs. Monotherapy leads to a better compliance and to less side effects compared to polytherapy. Therefore, the treatment process should be initiated with monotherapy and, if necessary, the treatment should be switched to polytherapy, and if inadequate, to other therapeutic modalities for epilepsy (Brodie and French, 2000; Brodie and Kwan, 2002). The efficacy is a function of the efficiency and of the tolerability (Kwan and Brodie, 2001).

Our study aimed to highlight the efficiency, the tolerability, the benefits of AEDs used in the patients with

*Corresponding author. E-mail: refahsayin@yyu.edu.tr. Tel: +90 505 217 87 69. Fax: +90 432 216 83 52.

partial and generalized epilepsy and to highlight the importance of the switching to surgical therapy in non-responders.

MATERIALS AND METHODS

The study, retrospectively, included 106 patients, who were hospitalized in the Neurology polyclinic between March 1996 and March 2003 and which were diagnosed with epilepsy. The patients were aged between 2 to 52 and were 61 females and 45 males. For every patient, physical and neurological examinations were performed; whole blood counts, biochemical tests (especially liver enzymes, fasting blood glucose, urea-creatinine and electrolyte values), electroencephalography (EEG) and, if required, sleep deprived and/or sleep EEGs were performed; magnetic resonance imaging (MRI) was taken and the drug blood levels were quantified. Of the 106 patients enrolled to the study, 73 (68.9%) were receiving monotherapy. Thirty-three patients (31.1%) were receiving polytherapy. In 1 patient to whom was added lamotrigine (ltg) and in 2 patients to whom gabapentine (gb) was added, three-drug combination was required. Four patients were operated by epilepsy surgeons. The patients that did not experience a seizure during the last six months and the patients that discontinued the therapy due to a 2-year seizure-free period (Baykan et al., 2011) were considered as "complete responders"; the patients that presented a reduction by at least 50% in the number of seizures were considered as "partial responders"; and the patients that showed a reduction by less than 50% in the number of seizures were considered as "non-responders". For the EEG examination of the cases, Neurofax 11 Analogue EEG device and Stellate system digital EEG device were used. For all the patients that participated to the study, sleep deprived, sleep and awake EEG were taken. For every patient, EEG was taken during the resting period and provocation methods such as the hyperventilation and the intermittent photic stimulation were applied. When evaluating EEG, the suitability of the EEG findings to the age, the epileptic property of the paroxysmal activity, the presence of activity in the epileptic focus and the dissemination of the epileptic focus to other sites were recorded. In the study, for the examination of MRI, 0.3 Tesla permanent magnet open MRI device was used.

Statistical analyses

The descriptive statistics for the earlier mentioned determinations were expressed as mean, standard deviation, minimum and maximum values and the categorical variables were expressed as number and percentage. Comparison of the group was made within the context of continuous variables. For this comparison, "one-way variance analysis (one-way ANOVA)" was used. To determine the association between the categorical variables, chi-square test was used. In the calculations, the statistical significance level was taken as 5% and statistical package for the social sciences (version: 13) was used as statistical package software.

RESULTS

The distribution of age and age group

The age range of the patients with epilepsy was between 2 to 52 years; mean age was 22.1 years for the patients with partial epilepsy and 18.7 years for the patients with generalized epilepsy.

Age groups

There were 35 patients in the age group of 0 to 16 years (children) (33%) and 71 patients in an age group above 16 (adults) (67%). There were 69 patients in the group with partial epilepsy and 37 patients in the group with generalized epilepsy. A correlation was found between the age groups and the distribution of gender ($p < 0.05$). While the pediatric group contained 16 male and 19 female patients, the adult group contained 29 male and 42 female patients. While, in the pediatric group 45.7% were males and 54.3% were females; in the adult group, 40.8% were males and 59.2% were females. Interestingly, both groups contained more female patients than male patients. A correlation was found between the age group and the duration of disease and the efficiency of the therapy ($p < 0.05$). The duration of disease was 1 to 2 years in 40%, 3 to 6 years in 37.1%, >6 years in 22.9% of the pediatric group and 1 to 2 years in 15.5%, 3 to 6 years in 33.8%, >6 years in 50.7% of the adult group. In the pediatric group, 8.6% did not respond to the therapy, 25.7% showed a partial response to the therapy, 62.9% showed a complete response to the therapy and the response of 2.9% was unknown. In the adult group, 15.5% did not respond to the therapy, 23.9% showed a partial response to the therapy, 38% showed a complete response to the therapy and the response of 22.5% was unknown. The pediatric group showed a better complete response to the therapy compared to the adult group.

The distribution of gender

In the patient groups, there were 61 female (57.5%) and 45 male (42.5%) patients. A statistically significant difference was found between the distribution of gender and the frequency of seizures and the protocol of therapy (monotherapy or polytherapy) ($p < 0.05$). The male patients, 66.7% were treated with monotherapy and 33.3% were treated with polytherapy. The female patients, comprising 70.5% were treated with monotherapy and 29.5% were treated with polytherapy. Among the male patients, the frequency of seizures was 4 or more per month in 36%, 1 to 3 per month in 63.3% and many times per year in 30.8%. Among the female patients, the frequency of seizures was 4 or more per month in 64%, 1 to 3 per month in 36.7% and many times per year in 69.2%.

The type of seizure

The cases were classified according to international league against epilepsy classification (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). In the patients with partial epilepsy, 8 simple partial seizures, 17 complex partial seizures and 44 secondary generalized seizures

Table 1. The types of seizure.

	cps	sgs	sps	gtc	myc	Absence	Atonic	Clonic	Total
Partial	17	44	8	0	0	0	0	0	69
Generalized	0	0	0	25	4	5	2	1	37
Total	17	44	8	25	4	5	2	1	106

cps: complex partial seizure; sgs: secondary generalized seizure with partial onset; sps: simple partial seizure; gtc: generalized tonic-clonic seizure; myc: myoclonic seizure.

with partial onset were present. In the patients with generalized epilepsy, 25 generalized tonic-clonic seizures, 4 myoclonic seizures, 5 absence seizures, 2 atonic seizures and 1 clonic seizures were present (Table 1). The types of seizures showed a correlation with the type of epilepsy ($p < 0.05$).

The type of epilepsy

Of the patients, 69 (65%) had partial and 37 (35%) had generalized epilepsy. The mean duration of disease was 2 ± 0.07 years. The duration of disease was 1 to 2 years in 23.6%, 3 to 6 years in 58.5% and more than 6 years in 41.5% of the patients. The duration of disease was 1 to 2 years in 20.3%, 3 to 5 years in 39.1% and more than 6 years in 60.6% of the patients with partial epilepsy and 1 to 2 years in 29.7%, 3 to 5 years in 27% and more than 6 years in 43.2% of the patients with generalized epilepsy. The type of epilepsy was found to have a correlation with the type of seizure, MRI, the protocol of therapy, therapeutical efficacy and the drugs used ($p < 0.05$). While complex partial seizures, simple partial seizures and secondary generalized seizures with partial onset showed a correlation with partial epilepsies; generalized tonic-clonic seizures, myoclonic seizures, absence seizures, atonic seizures and clonic seizures also showed a correlation with generalized epilepsy. On the MRI of the patients with partial epilepsy, 60.9% did not show any pathology and 39.1% showed a pathology (hippocampal atrophy, cortical dysplasia, encefalomalasic area etc.) On the MRI of the patients with generalized epilepsy, 83.8% did not show any pathology and 16.2% showed a pathology. This observation indicates that an underlying cause is more common in the patients with partial epilepsy compared to those with generalized epilepsy. Of the partial epilepsies, 63.8% are treated with monotherapy and 36.2% are treated with polytherapy; of the generalized epilepsies, 78.4% are treated with monotherapy and 21.6% are treated with polytherapy. This finding indicates that the patients with partial epilepsy are more refractory to the therapy compared to the patients with generalized epilepsy. Of the cases of partial epilepsy, 8.6% did not respond to the therapy, 20.3% showed a partial response to the therapy, 42% showed a complete response to the therapy and the

response of 21.7% was unknown. Of the cases of generalized epilepsy, 8.1% did not respond to the therapy, 32.4% showed a partial response to the therapy, 54.1% showed a complete response to the therapy and the response of 5.4% was unknown.

EEG findings

All patients had an EEG. While 87 patients (82.1%) showed epileptic discharges consistent with generalized and partial epilepsies, 19 (17.9%) did not show any pathologic findings on EEG. No statistical significant difference was found between the patients with and without pathology on EEG in terms of the efficacy of therapy ($p > 0.05$).

The results of antiepileptic therapy

The results of monotherapy

Of the 106 patients enrolled to the study, 73 (68.9%) were receiving monotherapy. Of these patients, 36 were receiving carbamazepine (cbz), 28 were receiving valproic acid (vpa), 8 were receiving oxcarbazepine (oxc) and 1 was receiving lamotrigine (ltg). The efficacy of the treatment was classified as "complete response", "partial response" and "no response". Of the patients that were receiving cbz, 21 (58%) showed complete response, 6 (17%) showed partial response and 9 (25%) showed no response. Of the patients that were receiving vpa, 17 (61%) showed complete response, 8 (29%) showed partial response and 3 (11%) showed no response. Of the patients that were receiving oxc, 6 (75%) showed complete response and 2 (25%) showed partial. One patient that was receiving ltg showed complete response.

The results of polytherapy

Thirty-three patients (31.1%) were receiving polytherapy. The drug and drug combinations used by the patients that were receiving monotherapy and polytherapy are given in Table 2. Of the patients that were receiving polytherapy, 14 (42%) showed complete response, 14 (42%) showed partial response and 5 (16%) showed no

Table 2. Antiepileptic drugs.

Groups	Treatment					Total
	cbz	vpa	ltg	oxc	Polytherapy	
par.	8	7	0	1	10	26
sec. gen.	16	6	1	4	15	42
gen.	12	15	0	3	8	38
Total	36	28	1	8	33	106

par: partial epilepsy; sec. gen.: secondary generalized epilepsy with partial onset; gen: generalized epilepsy; cbz: patients that use carbamazepine; vpa: patients that use valproic acid; ltg: patients that use lamotrigine; oxc: patients that use oxcarbazepine.

response. Among the 6 patients that were receiving vpa, ltg was added to the therapeutic regimen of 5 patients with partial epilepsy and topiramate (tpm) was added to the therapeutic regimen of 1 patient with generalized epilepsy. Among the 18 patients that were receiving cbz, vpa was added to the therapeutic regimen of 10 and ltg was added to the therapeutic regimen of 5 of 15 patients with partial epilepsy; and tpm was added to the therapeutic regimen of 2 and phenobarbital was added to the therapeutic regimen of 1 of 3 patients with generalized epilepsy. Of the patients that were receiving the combination therapy with cbz and vpa, 2 required three- and 1 required four-drug combination. Among the 9 patients that were receiving oxc, vpa was added to the therapeutic regimen of 2, ltg was added to the therapeutic regimen of 3 and gabapentine (gb) was added to the therapeutic regimen of 4 patients. In 1 patient to whom was added ltg and in 2 patients to whom gb was added, three-drug combination was required. The drugs used in monotherapy and polytherapy and the therapeutic efficacy and the duration of disease and the therapeutic efficacy showed a correlation ($p < 0.05$).

Results of MRI

While 73 patients (68.9%) showed normal MRI results, 33 (31.1%) showed a pathology on MRI. Of the patients that showed pathology, 9 had parahippocampal atrophy (2 bilateral and other 7 unilateral), 2 had unilateral arachnoid cyst, 9 had a variation of cavum septum pellucidum, 5 had advanced periventricular leukoplasia and cerebral atrophy, 5 had cerebral abscess, 1 had hamartoma consistent with tuberculosis, 1 had right mesial temporal sclerosis and 1 had heterotopy. A significant correlation was found between MRI and the therapeutic efficacy ($p < 0.05$). Of the patients that did not show any pathology on MRI, 11% showed no response, 23.3% showed partial response, 54.8% showed complete response and the type of response in 11% was unknown. Of the patients that showed a pathology on MRI, 18.2% showed no response, 27.3% showed partial response, 27.3% showed complete response and the type of response in 27.3% was unknown.

DISCUSSION

Epilepsy is the second most commonly chronic neurologic disorder encountered by neurologists after headache. In clinical practice, due to the difficulties experienced in the diagnosis and the classification of the epileptic seizures and epileptic syndromes as well as patient-based clinical course, a good evaluation and monitoring is required also for the therapy (Prasad et al., 1996; Kotagal and Rothner, 1993; Camfield and Camfield, 1996; Leppik and Wolff, 1993; Dichter, 1995; Bauer, 1997). Kwan et al., (2001) reported that the first AED given to 470 adult and pediatric patients with newly diagnosed partial seizures treated 47% of the patients. Of the patients, 83% was given cbz and the remaining was given vpa and ltg. The rate of a change of treatment due to adverse effects was higher in the patients that were given cbz (27%) compared to those that were given vpa (13%) and ltg (10%); and a complete resolution of seizure was most rarely seen with cbz. In this study, the authors reported that the seizures were completely resolved in 50% of the patients with newly diagnosed epilepsy, after the administration of monotherapy (Kwan and Brodie, 2001). In our study, the patients that were receiving cbz, 21 showed a complete response, 6 showed a partial response and 9 showed no response. Of the patients that were receiving vpa, 17 showed a complete response, 8 showed a partial response and 3 showed no response. As we had only one patient that was using ltg, we did not include ltg to the evaluation. There was no significant difference between the groups in terms of the drug efficacy based on the levels of cbz and vpa. Again, in our study, the rate of monotherapy was 46.2%, highlighting the importance of the monotherapy.

Ding et al. (2010) compared the efficacy of AEDs used in 389 children with retrospective generalized or unclassified seizures. For remissions until 1-year, vpa was found to be significantly better than either tpm or cbz ($p < 0.05$). For the subgroup with generalized onset epilepsy, vpa was much better than either tpm or cbz ($p < 0.05$). For unclassified epileptic seizures, no significant differences were found among the three AEDs. Vpa should be the drug of choice for children with generalized onset, and no significant differences were

found among the three AEDs in unclassified epileptic seizures (Ding et al., 2010).

Boldyreva et al. (2010) reported a retrospective observational investigation based on real clinical practice of relative efficacy of vpa, cbz and tpm. Authors have selected 106 adulthood patients (0 to 17years old) with a undoubted diagnosis of symptomatic or cryptogenic occipital lobe epilepsy (OLE). Efficacy of vpa in children with OLE was higher compared with cbz and tpm. In case of focal cortical dysphasia the efficacy of cbz was lower than vpa. In MRI-negative cases vpa was most effective (Boldyreva and Ermakov, 2010). In our study, 28 patients that were receiving vpa included 13 children and 15 adults. During the monotherapy of pediatric patients, 8 (61%) patients showed complete response, 3 patients showed a decrease of $\geq 50\%$ in seizure frequency and 2 patients did not show the desired response and were switched to another drug. Of these patients, 8 had generalized and 5 had partial seizures. Complete response was observed in 5 patients with generalized seizures and in 3 patients with partial seizures. The results were inadequate due to small number of cases. For adult patients, 9 (60%) showed a complete response to the treatment with vpa and 6 patients showed a decrease of $\geq 50\%$ in the seizure frequency. There were no patients without response. This finding implicated that our patients were effective in both adults and children, however, while two pediatric patients were switched to another drug due to absence of response, adult patients did not show such an observation. We had no pediatric or adult patient that received monotherapy with tpm and the treatment with tpm was given as a polytherapy. Our 36 patients that were using cbz included 13 children and 23 adults. Of these patients, 12 had generalized and 24 had partial seizures. Of our pediatric patients that were using cbz, 11 (85%) showed a complete response, 1 patient showed no response and another patient showed a decrease of $\geq 50\%$ in the seizure frequency. In our study, the response given to the monotherapy was 73% in pediatric patients and 52% in adult patients. This indicated the importance of monotherapy in our pediatric patients. Of the patients who did not indicate any pathology on MRI, 74% were treated with monotherapy and 26% was treated with polytherapy; of the patients with pathology, 57.6% was treated with monotherapy and 42.4% was treated with polytherapy.

Belousova et al. (2010) conducted a study on 254 children, with an age range of 11 months to 18 years, which had focal epilepsy and which were using oxc. The observation period was 31 weeks. The percentage of patients with a positive response to the oxc therapy (the decrease of seizure frequency by 50% and more) was 91.1%. The complete reduction of seizures was achieved in 59.4% of patients. In conclusion, oxc as the monotherapy is effective and well-tolerated in the treatment of focal epilepsies in the age groups studied (Belousova et al., 2010). In our study, 8 adult patients

used oxc as monotherapy. Six (75%) patients had complete response and 2 (25%) patients had partial response.

In the study performed by Arif et al. (2010) retrospectively, prescribed 10 different drugs commonly used for 417 patients of ≥ 55 years-old that were reported between 2000 and 2005. Without controlling for severity, lrg had the highest 12-month retention rate (79%), significantly higher than cbz (48%), gb (59%), oxc (24%), phenytoin (59%), and tpm (56%). The retention rate for levetiracetam (lev) (73%) was second highest and significantly higher than cbz and oxc. Oxc had the lowest retention rate, significantly lower than all other AEDs. lrg had the highest 12-month seizure-freedom rate (54%), followed by lev (43%). In this study, lrg was the most effective AED as measured by 12-month retention and seizure freedom, with lev a close second. Oxc was consistently less effective than most other AEDs (Arif et al., 2010). In our study, only one adult patient was receiving lrg and 8 patients were receiving oxc. The patient that was receiving lrg had a complete response. Of the patients that were receiving oxc, 6 had complete response and 2 had partial response. Although our study indicates that the treatment with oxc is efficient in adults, larger studies are needed for both lrg and oxc. None of our patients was using lev.

In the study performed by Bauer et al. (2009) treatment strategies for focal epilepsy need to take into account the phase and severity of the seizure disorder, co-morbidity, gender and age. Complete seizure control is most often achieved with AED monotherapy. If complete seizure control cannot be achieved with the first three steps of AED treatment, epilepsy surgery becomes the most likely treatment modality to provide complete seizure control (Bauer et al., 2009). In our study, in the patients with focal epilepsy, the seizures were firstly controlled with monotherapy and the seizures that could not be controlled with monotherapy were controlled with polytherapy and the seizures that could not be controlled with polytherapy were controlled with surgical therapy. This is important for the treatment protocol. Four patients were operated in our study, but we were not able to collect data of patients who have had surgery, because the patients after surgery did not come to follow-up.

Consequently, we concluded that the pediatric patients had complete response to monotherapy; that the patients with focal seizures had more focal finding on MRI compared to the patients with generalized seizures; that these patients were more refractory to the therapy and will require surgical therapy.

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