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Drug treatment failures and effectivity in children with newly diagnosed epilepsy

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ABSTRACT

Purpose: To determine the percentage of children whom first-line antiepileptic drug treatment failed and the specific reasons for the treatment failure in newly diagnosed epilepsy.
Methods: Hospital records were reviewed for 225 children who were newly diagnosed with epilepsy, started on the first antiepileptic drug, and then monitored for approximately 4.2 years.
Results: Of the 225 patients analyzed, the mean age was 7.9 ± 0.6 years at diagnosis. Most of the patients suffered from primarily generalized tonic-clonic seizures (in 84 patients, 37.3%). 114 patients (50.6%) were classified as having idiopathic epilepsy, 64 (28.4%) had symptomatic epilepsy and 47 (20.8%) has cryptogenic epilepsy. Valproic acid (*n*: 120, 53.3%), carbamazepine (*n*: 45, 20%) and oxcarbazepine (*n*: 31, 13.7%) were the most frequently prescribed antiepileptic drugs. Overall, 67.5% (*n*: 152) patients were treated successfully with the first antiepileptic drug. Seventy-three patients failed with the first-line antiepileptic drug. Of these patients, 28 discontinued medication because of adverse effects (38.3%), 26 because of lack of efficacy (35.6%) and 19 (26.02%)because of a combination of inefficacy and adverse effects. Age at diagnosis, seizure, etiology and antiepileptic drug selection are considered to be associated with drug treatment failure in childhood epilepsy. There was no statistically significant effect of any of these variables on first-line treatment outcome.
Conclusion: Approximately one-third of the children with newly diagnosed epilepsy fail the first prescribed antiepileptic drug. Adverse effects and lack of efficacy contributed equally to the treatment failures.

1. Introduction

Epilepsy is a group of neurologic conditions characterized by recurrent, unprovoked seizures. A large proportion of epilepsy begins in childhood. The prevalence of epilepsy in children has been estimated at 3.5–7.2 per 1000 children.[1] Many types of epilepsy occur in children, with diagnosis depending on the type of seizure (simple partial, complex partial, partial becoming generalized, generalized) and etiology (symptomatic, idiopathic, cryptogenic). The aim of antiepileptic drug treatment is to reduce epilepsy seizure frequency with as few side effects while minimising long-term detrimental effects. Knowing the response to antiepileptic drug treatment will undoubtedly influence the treatment strategy in childhood epilepsy. Data on why children fail medications would allow better counseling of patients and parents as well. There are relatively fewer studies examining the tolerability and treatment failure of antiepileptic drugs in children compared with adults. We provide a comprehensive and current literature review of the AEDs, focusing on treatment failure and tolerability data in children. Previous studies have yielded data for adults suggesting that fewer than one half of patients become seizure free with the first-line antiepileptic drug tried,[2–6] whereas antiepileptic drug treatment failure and reasons in children is virtually unknown and few data address this issue specifically.[7–9] Camfield et al. documented success or failure of the initial AED in the first year of treatment, as well as long-term seizure control and remission. They showed that, overall, in 17% of children the treatment with the first medication failed, and treatment failures of up to 24% were more common in those with partial seizures (compared with generalized tonic/clonic seizures).[7] Dudley et al. found that treatment with the first antiepileptic drug failed in 31.6% of the children.[9] An audit of childhood antiepileptic drug use over a 4-year period in the Netherlands found a 40% failure rate with the first antiepileptic drug prescribed.[8]

In clinical practice, it would be desirable to better predict the effectivity of the antiepileptic drug within a short period after diagnosis. Because studies on the treatment failure and tolerability of the first antiepileptic drug in children are very rare, the present retrospective study was designed with the objective of determining the percentage of children whom first-line antiepileptic drug treatment failed and the specific reasons for the treatment failure.

2. Methods

2.1. Patients and treatment

The study group was identified from the patient charts of Pediatric Neurology Department of Gazi University Faculty of

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Medicine in Ankara. The target population consisted of all patients who were followed by well-established diagnosis of epilepsy as defined by the International Classification of Epilepsies and Epileptic Syndromes[10] and treated with the antiepileptic drugs for the first time. We retrospectively reviewed through the records of a total of 225 patients aged 0–18 years who were newly diagnosed with epilepsy and prescribed an antiepileptic drug during the period from January 2000 to December 2004. Children who were not treated nor followed for epilepsy, children who had started treatment elsewhere but came to our center for follow-up and those diagnosed with febrile seizures were not included in the chart review. In the study hospital, when the children are diagnosed with epilepsy, they are followed at our clinic until they achieve seizure remission and are taken off treatment. To determine if and why patients failed the first-line antiepileptic drug prescribed, the hospital records of these children were reviewed for an average of 4.2 years. Seizure freedom was defined as having no more seizures for the 4.2-year duration of this study or had no seizures for an adequate period of time (i.e., 2 years). The first prescribed antiepileptic drug was considered as a treatment failure if (1) it does not seem to control seizure to a significant degree (lack of efficacy)[2] causes intolerable adverse effects. If the antiepileptic drug decreased seizure frequency to some reasonable degree but not entirely without causing intolerable adverse effects, the drug was not considered a treatment failure. The Gazi University Faculty of Medicine Institutional Review Board approved this study.

Detailed chart review of the patient's included age, sex, diagnosis, seizure type, etiology, medication dose and duration of treatment, the reason for discontinuation of the drug and adverse effects experienced. The results of any electroencephalography or brain imaging were recorded. Etiology was defined according to the quidelines of the International League Against Epilepsy.[10] The percentage of patients who failed initial treatment and the reason for each treatment failure was determined. Association between the percentage of each failed drugs and age at onset, seizure types, etiology was determined.

2.2. Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences software, version 11.5 (SPSS Inc., Chicago, IL, 2002). Data were reported as means with standard error. The major objective of the study was to study the interaction among drug treatment failure rates, effectiveness of the first antiepileptic drug prescribed in newly diagnosed pediatric epilepsy. Differences between number of patients in various subgroups were compared using chi-square test, and group means were compared using unpaired two-tailed *t*-tests. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Clinical features

Between January 1, 1999, and December 30, 2005, a total of 502 children were admitted to the Gazi University Pediatric Neurology Department for seizures. 183 were febrile seizures, 85 were seen at another clinic for seizure before and drug was started. Upon being seen in clinic, 234 patients were newly diagnosed with epilepsy and started on an antiepileptic drug. The charts of these patients were reviewed for 5.3 years. Nine patients were lost to follow-up. Eventually, 225 patients remained for the analyses.

Table 1
Characteristics of the patients treated with first-line antiepileptic drug.

Characteristics	Seizure-free group	Failure group	Total	*p*
Patients enrolled, *n* (%)	152 (67.5)	73 (32.4)	225	
Demographic characteristics				
Male, *n*(%)	81 (53.2)	41 (56.1)	122	0.965
Female, *n* (%)	71 (46.7)	32 (43.8)	103	0.971
Age (years)				
Median (range)	8	7.5	7.5	
Mean (SD)	8.2 (0.6)	7.6 (0.8)	7.5 (0.6)	0.423
Age groups				0.375
<1, *n* (%)	14 (63.6)	8 (36.3)	22	
1–6, *n* (%)	42 (75)	14 (25)	56	
6–12, *n* (%)	58 (73.5)	21 (26.5)	79	
>12, *n* (%)	38 (55.8)	30 (44.2)	68	
Clinical details				
Seizure type				0.745
CPS with sec. generalization	31 (25.6)	18 (24.6)	49 (21.7)	
Primarily generalized tonic clonic	57 (37.5)	27 (36.9)	84 (37.3)	
CPS without sec. generalization	14 (9.2)	7 (9.5)	21 (9.3)	
Absence	20 (13.1)	12 (16.4)	32 (14.2)	
Myoclonic	13 (8.5)	2 (2.7)	15 (6.6)	
Infantile spasms	5 (3.2)	13 (17.8)	18 (8)	
Undetermined	4 (2.6)	2 (2.7)	6 (2.6)	
Etiology				0.664
Idiopathic	78 (51.2)	36 (49.3)	114 (50.6)	
Cryptogenic	46 (30.2)	18 (24.6)	64 (28.4)	
Syptomatic	31 (20.3)	16 (21.9)	47 (20.8)	
Treatment details				
Antiepileptic drug used				0.856
Valproic acid	84 (55.2)	36 (49.3)	120 (53.3)	
Carbamazepine	33 (21.7)	12 (16.4)	45 (20)	
Oxcarbazepine	22 (14.4)	9 (12.3)	31 (13.7)	
Others	18 (11.8)	11 (15)	29 (12.8)	
Antiepileptic drug dosage (mg/kg per day)				
Valproic acid	22.6 ± 3.4	18.5 ± 2.9	21.9 ± 2.6	0.432
Carbamazepine	13.9 ± 1.4	13.7 ± 1.5	13.8 ± 1.2	0.927
Oxcarbazepine	27.3 ± 4.1	23.5 ± 3.5	25.6 ± 4.1	0.456

Table 1 demonstrates the characteristics of the patients included in the study. More than 86% of the patients attended the clinic for 3.5 years, with follow-up periods ranging from 18 to 72 months. Of the 225 patients analyzed, there were 122 boys (54.2%), and the mean age of the group was 7.9 ± 0.6 years at diagnosis. Most of the patients suffered from primarily generalized tonic-clonic seizures (in 84 patients, 37.3%). The other seizure types encountered were complex partial seizures with secondary generalization (in 49 patients, %21.7), absence seizures (in 32 patients, 14.2%), complex partial seizures without secondary generalization (in 21 patients, 9.3%), infantile spasm (in 18 patients, 8%), myoclonic (in 15 patients, 6.6%), undetermined (in 6 patients, 2.6%). In addition, 114 patients (50.6%) were classified as having idiopathic epilepsy, 64 (28.4%) had symptomatic epilepsy and 47 (20.8%) has cryptogenic epilepsy.

3.2. Treatment

Valproic acid (*n*: 120, 53.3%), carbamazepine (*n*: 45, 20%) and oxcarbazepine (*n*: 31, 13.7%) were the most frequently prescribed antiepileptic drugs. Other first-line medications used were phenobarbital, clobazam, lamotrigine and vigabatrin. Concomitant antiepileptic drugs used were topiramate, levatiracetam, ethosuximide and clobazam.

3.3. Treatment failures

Overall, 67.5% (*n*: 152) patients were treated successfully with the first antiepileptic drug. Sixteen (7.1%) patients were added on adjunct antiepileptic drugs without stopping the first antiepileptic drug to achieve a better seizure control during follow-up. In these patients, the first prescribed antiepileptic drug did not totally stop seizures but decrease seizure frequency, therefore these patients were not considered treatment failures.

The successfully treated group was compared to the failed group in terms of age at seizure onset, seizure type, antiepileptic drug used and drug dose.

A higher proportion of patients with symptomatic and cryptogenic epilepsy had to discontinue the first prescribed antiepileptic drug because of either intolerable side effects or lack of efficacy, compared with patients with idiopathic epilepsy (symptomatic vs. idiopathic:14.1% vs. 4.3%; *p*: 0.004; cryptogenic vs. idiopathic:8.5% vs. 4.3%; *p*: 0.04) (data not shown).

No statistically significant differences were seen between two groups in terms of age at seizure onset, antiepileptic drug used and drug dose.

3.4. Reasons for treatment failures

Certain age groups (children with seizure onset within the first year), seizure types (infantile spasms, myoclonic, atonic), etiology (idiopathic, symptomatic, cryptogenic) and antiepileptic drug selection are considered to be associated with drug treatment failure in childhood epilepsy.

Seventy-three patients failed with the first-line antiepileptic drug. Of these patients, 28 discontinued medication because of adverse effects (38.3%), 26 because of lack of efficacy (35.6%) and 19 (26.02%) because of a combination of inefficacy and adverse effects. Most common adverse event was rashes, which developed more often with carbamazepine and carbamazepine was discontinued. For valproate, the most frequent side effects causing drug discontinuation were weight gain and behavioral problems. Tiredness and dizziness was the most often adverse effect for oxcarbazepine (Table 2). The rate of discontinuation because of adverse events was lower among patients on oxcarbazepine but it was not statistically significant.

Table 2
Adverse effects leading to antiepileptic drug failure for the three most commonly prescribed drugs.

Adverse effect	Valproic acid	Carbamazepine	Oxcarbazepine
Increased appetite/weight gain	6	0	0
Rash	0	12	3
Tremor	2	0	0
Headache	1	4	2
Learning problems	1	1	0
Nausea/vomiting	2	3	0
Change in mood	2	2	1
Decreased attention	2	1	0
Tiredness or drowsiness	2	0	1
Somnolence	0	2	1
Dizziness	0	3	2
Hair loss	2	0	0
Thrombocytopenia	1	0	0
Ataxia	1	0	0
Hyponatremia	0	3	1
Total adverse events[a]	22	31	11
Number of patients drug discontinued[**]	15	24	8

[a] Some patients experienced more than one adverse effect.
[**] Carbamazepine versus valproic acid, *p*: 0.073; versus oxcarbazepine, *p*: 0.051.

3.5. Age at diagnosis and treatment failures

We compared the treatment failure rates at different age groups. For the group who failed the first-line drug, there was an inclination toward aged less than 1 year at diagnosis. There were fewer children aged more than 10 years at diagnosis. But there was not a statistically significant difference between age groups (chi-square analysis, *p*: 0.375) (Table 1).

3.6. Comparison of antiepileptic drugs

Valproic acid, carbamazepine and oxcarbazepine were compared among the children with treatment failure. There was no statistically significant group between the number of failures for each medication (*p*: 0.856). Failure rate was 30%, 26.6%, 29% for valproic acid, carbamazepine and oxcarbazepine, respectively. Eleven treatment failures occurred in patients treated with other antiepileptic drugs other than valproic acid, carbamazepine and oxcarbazepine. All were attributed to lack of efficacy.

Dose of the antiepileptic drug used could also affect the efficacy. The majority of seizure-free patients used only a moderate daily dose (valproic acid, 22.45 ± 5.67 mg/kg; carbamazepine, 14.78 ± 5.03 mg/kg; oxcarbazepine 31.56 ± 7.78 mg/kg). Dosages were also compared for children with treatment in terms of adverse effects, lack of efficacy or a combination of both factors (Table 1). There was no significant difference in the doses between seizure-free patients using valproic acid, carbamazepine and oxcarbazepine and those who had to change treatment because of intolerable adverse effects in all three antiepileptic drugs. Although the difference did not reach significance, patients who became seizure free took slightly lower doses than those with the treatment failures because of adverse effects for all three antiepileptic drugs. In contrast, the children with drug treatment due to lack of efficacy, the drug doses were slightly higher.

3.7. Effects of specific seizure types and etiology

There was no significant difference (*p*: 0.664) in the drug treatment failure rates between the idiopathic, symptomatic and cryptogenic groups. There was also no statistical significance between the etiology groups in the proportion of patients who continued the first drug.

Likewise, no statistically significant difference were found by analysis for seizure type (*p*: 0.745) (Table 1).

4. Discussion

Childhood epilepsy in our clinical practice had a generally favorable outcome, with two-thirds of children achieving remission with the first antiepileptic drug prescribed. Although there are many studies dealing with the treatment failure of the first antiepileptic drug in adults, few studies have assessed the drug treatment failure rates and effectiveness of the first antiepileptic drug in children. Previous studies have reported that the first-line antiepileptic drug will eventually be effective in seizure control in 67–80% of the children.[7,9]

The present study has two main findings. The first is that in approximately 30% of the patients first-line antiepileptic drug treatment failed. The second finding is that adverse events and lack of efficacy contributed equally to the drug failure.

4.1. Treatment failure rate

Nearly two-thirds of the patients became seizure free and 32% failure rate was found with the first prescribed antiepileptic drug. Previous studies have largely agreed with this finding.[2,7,9,11] Carpay et al. found 40% of children not responding successfully for the first antiepileptic drug.[8] Kwan and Brodie reported a failure rate less than 50% for patients of all ages, including the 9.8% of their patient population who were between 9 and 15 years.[2] Camfield et al. obtained more hopeful results for children for whom their first AED failed. They reported a 20% drug treatment failure rate over the first year.[7] It should be underlined that Camfield included only children with generalized tonic clonic, partial and partial with secondary generalized seizures and did not include treatment failures due to adverse effects. Therefore, we cannot compare our results with Camfield directly. Similar findings, however, have been reported in trials by Ma et al. and Dudley et al. recently.[9,11] Ma et al. studied a group of 520 children aged $<$18 years and investigated the interaction among efficacy, tolerability and overall effectiveness of the first antiepileptic drug in children with newly diagnosed epilepsy. Overall, 66.2% of the children became seizure free with the first prescribed antiepileptic drug.[11] Dudley et al. assessed the percentage of children for whom antiepileptic drug treatment fails and specific reasons for treatment failures. They found that treatment with the first antiepileptic drug failed in 30/95(31.6%) children.[9] Moreover, further clinical studies are needed to validate our observations.

4.2. Antiepileptic drugs

In the present study, valproate, carbamazepine and oxcarbazepine were the most commonly prescribed antiepileptic drugs. All have similar effectiveness and failure rates. The percentages of patients who changed the first-line antiepileptic drugs both using valproate, carbamazepine and oxcarbazepine are not significantly different. Although the difference is not statistically significant, patients who became seizure free took lower doses than those with drug treatment failures because of adverse effects. This represents the common clinical observation. AED doses are usually progressively increased in patients experiencing ongoing seizures. Therefore, it is not surprising that they received a higher dose compared with the seizure-free patients. Those who had adverse events due to the antiepileptic drugs took a lower dose than the responding patients, as the majority of withdrawals due to adverse events occurred at relatively low dosage for all three AEDs. The reasons for such marked differences are not completely understood. This may be due to the diversity of underlying neuropathologies[12,13] and possible genetic variability influencing drug response and tolerance.[14] These data also support the suggestion of two distinct populations of patients with newly diagnosed epilepsy [i.e., those responding to monotherapy and those requiring treatment with more than one AED[15]].

To the best of our knowledge, the present study is the first one which provided data on treatment failures with a newer antiepileptic drug, oxcarbazepine. Although statistically not significant, our data may indicate that oxcarbazepine may be better tolerated than the standard antiepileptic drugs with equivalent efficacy. Comparative trials should be performed on the failure rates and reasons for failures of newer antiepileptic drugs in childhood epilepsy.

4.3. Reasons for drug treatment failure

In the present study, we observed no difference in the proportion of treatment failure due to adverse effects, lack of efficacy, or the combination of these. The data we found are compatible with those reported in previous studies.[2,9] Kwan et al. studied both children and adults. Dudley et al. also found that adverse effects and lack of efficacy contributed equally to first-line antiepileptic treatment failures in newly diagnosed epilepsy in children.[9] The population we reported on here constituted only pediatric patients. The proportions that we observed were more similar to those reported by Dudley et al. The most frequent adverse effect of carbamazepine treatment necessitating drug discontinuation was rash. Increased weight gain and behavioral problems were the most frequent adverse effects among patients using valproate. No deaths or life threatening adverse events occurred during the course of this study. Our data indicate that adverse events were frequent but not severe, and were one of the main reasons for withdrawal from AED monotherapy.

Variables predictive of the drug treatment failure in childhood epilepsy were etiology, seizure type and age at onset. Our findings were similar to the previous studies.[2,9] Dudley et al. found age at onset below 1 year is associated with treatment failure. Our group of patients younger than 1 year also showed an inclination toward treatment failure. Although the results were not statistically significant, only the influence of age seemed to be correlated with drug treatment failure.

4.4. Limitations of the study

The main limitation of the study is its retrospective design. In our center, we increase drug dosage to the maximal recommended dose or to the point at which the patient showed signs of toxicity before consider it ineffective. After the drug is accepted as ineffective, the pediatric neurologist stops the drug because of lack of efficacy. Antiepileptic drug levels were not routinely measured, and specific maximal dose guidelines were not used for this study. However, it may be possible that some patients may have tolerated a further increase in dose. If antiepileptic drugs were discontinued prematurely in a small number of subjects, the success rate for the first prescribed antiepileptic drug may be higher than we found.

5. Conclusion

To the best of our knowledge, this is the first study that assesses the efficacy and treatment failure rate of older antiepileptic drugs; valproate and carbamazepine and a newer antiepileptic drug; oxcarbazepine in a large group of pediatrics patients with newly diagnosed epilepsy. The rate of drug discontinuation because of adverse events was lower among patients on oxcarbazepine but it was not statistically significant. 32.5% of the children with newly diagnosed epilepsy fail the first prescribed antiepileptic drug. Adverse effects and lack of efficacy contributed equally to the treatment failures. Although our understanding of the treatment of childhood epilepsy has improved over the last two decades, much

work lies ahead in this field. Future longitudinal prospective multicenter studies are needed to assess the outcome of antiepileptic drug treatment. A better understanding of the natural history of treated epilepsy would allow more accurate assessment of the factors influencing drug treatment failure in pediatric epilepsy and help formulate a strategic approach to management in patients in whom monotherapy with the first-choice AED fails.

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