Seizure 23 (2014) 252–259

Contents lists available at ScienceDirect

Seizure

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

Efficacy and tolerability of the first antiepileptic drug in children with newly diagnosed idiopathic epilepsy

Ünsal Yılmaz [a,*], Tuba Sevim Yılmaz [b], Gülşen Dizdarer [a], Gülçin Akıncı [a], Orkide Güzel [a], Hasan Tekgül [c]

[a] Department of Pediatric Neurology, Dr. Behçet Uz Children's Hospital, Izmir, Turkey
[b] Department of Public Health, Dokuz Eylul University Hospital, Izmir, Turkey
[c] Department of Pediatric Neurology, Ege University Hospital, Izmir, Turkey

ARTICLE INFO

Article history:
Received 15 October 2013
Received in revised form 18 November 2013
Accepted 2 December 2013

Keywords:
Epilepsy
Antiepileptic drugs
Treatment failure
Efficacy
Tolerability
Children

ABSTRACT

Purpose: Limited data are available for the effectiveness of the antiepileptic drugs in children in daily clinical practice. The aim of this study was to investigate the efficacy and tolerability of the first prescribed old and new antiepileptic drugs in children with newly diagnosed idiopathic epilepsy during a 12-month period.

Method: A total of 289 children (141 females and 148 males) who received phenobarbital ($n = 33$), valproate ($n = 142$), carbamazepine ($n = 42$), oxcarbazepine ($n = 38$), or levetiracetam ($n = 34$) as the first-line treatment, were enrolled in the study. Seizure control and the occurrence of adverse events were assessed during a treatment period of 12 months.

Results: Overall, 245 (84.8%) patients remained seizure-free during the study period. The rate of seizure control did not differ significantly between the drug groups ($p = 0.099$). Forty-four (15.2%) patients including 1 (3.0%) treated with phenobarbital, 22 (15.5%) with valproate, 7 (16.7%) with carbamazepine, 10 (26.3%) with oxcarbazepine, and 4 (11.8%) with levetiracetam had treatment failure. There was no significant difference between seizure-free and failure groups in terms of age, gender, seizure type, and drugs used. Overall, 80 (27.7%) patients had adverse events, of those the most common ones were behavioral problems, nausea and/or vomiting, weight gain, and learning difficulties. The reasons for treatment failures were lack of seizure control in 29 (10.0%) patients and intolerable adverse events in 15 (5.2%) patients.

Conclusion: It appears that old (phenobarbital, valproate and carbamazepine) and new antiepileptic drugs (oxcarbazepine and levetiracetam) have similar efficacy and tolerability profiles.

Institutional ethic number is 28.3.2013/14.

1. Introduction

Epilepsy is the most common chronic neurologic disorder that requires long-term medication in children. Its prevalence has been estimated at 0.5–1% in children.[1,2] Prior to 1993, the choice of AEDs was limited to old antiepileptic drugs (AEDs) (phenobarbital, primidone, phenytoin, carbamazepine, valproate and ethosuximide). Among them, valproate, carbamazepine and phenobarbital are effective and more widely used medications for the treatment of many types of epilepsy.[3] Since 1993, 11 new AEDs (felbamate, oxcarbazepine, gabapentin, lamotrigine, topiramate, levetiracetam, tiagabine, vigabatrin,pregabalin, rufinamide, zonisamide, and lacosamide) have been introduced to the market. Because of the lack of data on the efficacy and safety of the new AEDs, their applications depend on the clinicians' own experiences. Levetiracetam and oxcarbazepine are the new generation AEDs, that are increasingly used as monotherapy as well as add-on therapy in children.[4,5] However, treatment failure due to lack of seizure control or intolerable adverse effects remains the major consequences in children suffering from epilepsy.

The pharmacokinetics of AEDs in pediatric population differ considerably from those of adults.[6] Although it has been suggested that the efficacy of AEDs in adults could be used to predict the efficacy of AEDs in the pediatric population,[7] effectiveness of old and new AEDs in everyday child neurology practice has not been

Abbreviation: AED, Antiepileptic drug.

* Corresponding author at: Dr. Behçet Uz Children's Hospital, Department of Pediatric Neurology, Alsancak, İzmir 35210, Turkey. Tel.: +90 532 7163537; fax: +90 232 4892315.
E-mail addresses: drunsalyilmaz@yahoo.com (Ü. Yılmaz), tuba.yilmaz@deu.edu.tr (T.S. Yılmaz), gdizdarer@yahoo.com (G. Dizdarer), akincigulcin@gmail.com (G. Akıncı), orkideege@hotmail.com (O. Güzel), hasan.tekgul@ege.edu.tr (H. Tekgül).

1059-1311/$ – see front matter © 2013 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.seizure.2013.12.001

well-described, likely due to legal and ethical restrictions in performing randomized controlled trials establishing the efficacy of a new AED.

In adults with newly diagnosed epilepsy, approximately one half of patients become seizure free with the first prescribed AED.[8–10] In limited studies that addressed this issue in children, the effectiveness rates have been reported between 60 and 80%.[11–14] The main reasons for treatment failures are lack of efficacy and intolerability due to adverse effects.[13] While some studies have demonstrated that the most commonly used AEDs including valproate, carbamazepine and phenobarbital were found to be equivalent in terms of seizure control and adverse effects,[14,15] others reported significant differences between the drug groups.[3,16] Moreover, data on effectiveness of new AEDs including oxcarbazepine and levetiracetam have been more limited.[17–19]

In the present study, we aimed to investigate the efficacy and tolerability of old and new AEDs in children with newly diagnosed idiopathic epilepsy when used as a first-line treatment.

2. *Materials and* methods

Hospital charts of children (ranging from 1 month to 18 years), who admitted to pediatric neurology out-patient clinic at Dr Behçet Uz Children's Hospital between July 01, 2011 and May 01, 2013, were retrospectively reviewed. Children with newly onset idiopathic epilepsy, who were initiated with phenobarbital, valproate, carbamazepine, oxcarbazepine, or levetiracetam monotherapy, were included if data were available regarding a follow-up period of 12 months. Patients were excluded from the study if they were diagnosed with symptomatic or cryptogenic epilepsy, those previously received antiepileptic drug therapy or if they had less than one seizure per year prior to treatment. Patients with evidence of persistent nonadherence to medication therapy, those using more than one AEDs, those with documented pseudoseizures, and those with concurrent neurologic or other chronic disorders were excluded. Patients who were diagnosed with drug resistant epilepsy during a twelve month follow-up period after the first drug failure were also excluded in order to eliminate the impact of that some of the AEDs might have been chosen for patients with more severe epilepsy, which, in turn, might have them labeled incorrectly as less effective. Newly onset epilepsy was defined as two or more unprovoked seizures. Drug resistant epilepsy was defined as failure of adequate trials of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[20] Institutional Ethical Commitee approved the study.

Each child was assessed with a standardized work-up and follow-up, and all the demographic, clinical, laboratory, electroencephalographic and radiologic results were recorded into a standardized form. Following a thorough history, a detailed physical and neurologic examination was performed, and electroencephalography and magnetic resonance imaging (MRI) of the brain were obtained. Antiepileptic drugs were selected by the doctors on the basis of their experience and largely according to the International League Against Epilepsy (ILAE) recommendations.[21] Initial doses of AEDs were titrated to the maximal limit of tolerability in patients still reporting seizures. Detailed information including age, diagnosis, sex, birth history, past and family history of the patients, type of seizures, etiology of seizures, and epilepsy syndrome, electroencephalography and imaging results, and selected AEDs were collected. Seizure types, etiology and epilepsy syndromes were classified according to the International League Against Epilepsy Proposal for Revised Classification of Epilepsies and Epileptic Syndromes.[22] The patients diagnosed with epilepsy that do not fit any defined syndromes, patients with generalized epilepsy with febrile seizures plus and patients with frontal lob epilepsy were also included into the study if the patients had no known or presumptive underlying metabolic or structural cause of epilepsy.

Patients were considered to be seizure-free if they had no more seizures for at least 12 months on a stable dose in monotherapy or breakthrough seizures only with missed doses of medication. A first-drug treatment failure was defined discontinuation of the AED due to lack of seizure control despite being able to tolerate the medication in maximum doses (lack of efficacy), or intolerable adverse events. At our hospital, if the medication controls seizures to a reasonable degree, but not entirely at the maximal therapeutic dose without causing adverse effects, normally an adjunct AED is added to the first drug, instead of changing the drug altogether; and if seizures stop for a reasonable period, the first antiepileptic drug then tapered. In these cases, also, the first drug was considered as a treatment failure in the present study.

Tolerability and adverse events were assessed by documenting adverse events spontaneously reported by the parents or the children. Adverse events were classified as major and minor events according to their severity. Major adverse events were defined as events leading to cessation of AEDs. Weight gain was considered major adverse event when the patients gained more than 10% of their pre-treatment weight or when it caused intolerable anxiety. Adverse events which were tolerated by modification of the dosing scheme, symptomatic or supportive management, or behavioral modification were considered minor adverse events. Adverse psychiatric events including irritability, hyperactivity, agitation, and aggressive behavior were grouped as behavioral or personality changes. Adherence was assessed by direct questioning, physical examination and by measurement of serum drug concentrations for phenobarbital, valproate and carbamazepine.

Children were monitored at the first month after the beginning of drug therapy and at every three months subsequently. At each visit, seizure response, adverse events, medication dose and duration of use, the reason for medication discontinuation, adherence, and random serum levels were recorded. The overall percentage of patients who failed initial treatment, and the reason for each treatment failure were determined. Then, the percentage of failed treatments was analyzed in terms of the AED used, the patient's age, and seizure types to examine how these factors influence first-line treatment options.

2.1. Statistics

The data were analyzed using SPSS for Windows software package, version 20.0 (SPSS, Chicago, IL). Continuous variables were expressed as means ± standard deviations. Pearson's chi-square test or Fisher's exact test was used, as appropriate, for analysis of between-group differences in discrete variables, and analysis of variance (ANOVA) with a Bonferroni post hoc test was used for continuous variables. Significance was set at the $p < 0.05$ level in analysis.

3. Results

3.1. Patients

A total of 572 children diagnosed with newly onset epilepsy were identified. Of them, those with symptomatic or cryptogenic epilepsy ($n = 119$), those with less than 12 month-period of follow-up ($n = 112$), patients who developed drug resistant epilepsy after the first drug failure ($n = 25$), and patients who were lost to follow-up ($n = 27$) were excluded from the study. The data of 289 children with newly diagnosed idiopathic epilepsy who received AED monotherapy for at least 12-month period were analyzed. Demographic characteristics of subjects are presented in Table 1. Of 289 children, 33 (11.4%) received phenobarbital, 142