Epilepsy & Behavior 61 (2016) 34–40

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

High-dose versus low-dose valproate for the treatment of juvenile myoclonic epilepsy: Going from low to high☆

Laura E. Hernández-Vanegas [a], Aurelio Jara-Prado [b], Adriana Ochoa [b], Nayelli Rodríguez y Rodríguez [c], Reyna Durón [d], Daniel Crail-Meléndez [e], Ma. Elisa Alonso [b], Antonio V. Delgado-Escueta [f,g], Iris E. Martínez-Juárez [a,*]

[a] National Institute of Neurology and Neurosurgery of Mexico, Epilepsy Clinic, Mexico
[b] National Institute of Neurology and Neurosurgery of Mexico, Neurogenetics and Molecular Biology Department, Mexico
[c] Benemérita Universidad Autónoma de Puebla, Mexico
[d] Universidad Tecnológica Centroamericana (UNITEC), Tegucigalpa, Honduras
[e] National Institute of Neurology and Neurosurgery of Mexico, Neuropsychiatry Unit, Mexico
[f] Epilepsy Genetics/Genomics Laboratories and Epilepsy Center of Excellence, Neurology and Research Services, VA GLAHS, Los Angeles, CA, United States
[g] David Geffen School of Medicine at UCLA, Los Angeles, CA, United States

ARTICLE INFO

Article history:
Received 19 January 2016
Revised 28 April 2016
Accepted 29 April 2016
Available online xxxx

Keywords:
Blood level
Valproate
Juvenile myoclonic epilepsy
Antiepileptic drugs
Epilepsy/seizures
Dose

ABSTRACT

Juvenile myoclonic epilepsy (JME) is a genetic generalized epilepsy accounting for 3–12% of adult cases of epilepsy. Valproate has proven to be the first-choice drug in JME for controlling the most common seizure types: myoclonic, absence, and generalized tonic–clonic (GTC). In this retrospective study, we analyzed seizure outcome in patients with JME using valproate monotherapy for a minimum period of one year. Low valproate dose was considered to be 1000 mg/day or lower, while serum levels were considered to be low if they were at or below 50 mcg/dl. One hundred three patients met the inclusion criteria. Fifty-six patients (54.4%) were female. The current average age was 28.4 ± 7.4 years, while the age of epilepsy onset was 13.6 ± 2.9 years. Most patients corresponded to the subsyndrome of classic JME. Forty-six (44.7%) patients were free from all seizure types, and 76 (73.7%) patients were free from GTC seizures. No significant difference was found in seizure freedom among patients using a low dose of valproate versus a high dose ($p = 0.535$) or among patients with low blood levels versus high blood levels ($p = 0.69$). In patients with JME, it seems appropriate to use low doses of valproate (500 mg to 1000 mg) for initial treatment and then to determine if freedom from seizures was attained.

1. Introduction

Juvenile myoclonic epilepsy (JME), previously called idiopathic generalized epilepsy, is a genetic generalized epilepsy (GGE), currently classified by the International League Against Epilepsy (ILAE) as an electroclinical syndrome [1]. Juvenile myoclonic epilepsy appears around puberty and is characterized by seizures with bilateral, single, or repetitive arrhythmic, irregular myoclonic jerks, predominantly in the arms, without disturbance of consciousness. Often, there are generalized tonic–clonic (GTC) seizures and, less often, infrequent absences. Juvenile myoclonic epilepsy is a very common, if not the most common, form of GGE, accounting for 3% (population-based prevalence) to 12% (clinic- and hospital-based prevalence) of cases [2,3].

In the original cohort of 47 patients studied by Janz and Christian, treatment with barbiturates provided satisfactory control of "petit mal and grand mal seizures" [4]. Barbiturates were the treatment of choice until 1984, when valproate (VPA) was reported for the first time to have remarkable potency in JME [5,6]. Other drugs presently considered suitable for treatment of JME are clonazepam [7], lamotrigine (LTG) [8–10], levetiracetam (LEV) [11], topiramate [12–14], phenobarbital (PB), and zonisamide (ZNS) [15]. Lacosamide (LCS) has not shown effectiveness in JME [16].

Over the years, VPA has proven to be the first-choice drug for JME, with restrictions in women of childbearing age. A prospective randomized trial in patients with GGE showed more effectiveness and better tolerance with VPA compared with that with LTG and TPM [17–20].

☆ Statistical analysis conducted by Iris E. Martinez-Juarez, MD, MSc and Daniel Crail-Meléndez, MD, MSc.

* Corresponding author at: National Institute of Neurology and Neurosurgery, Mexico City, Insurgentes Sur 3877, Col. La Fama, Del. Tlalpan, Mexico City 14269, Mexico. Tel.: +52 55 56063822x2052.
E-mail address: imartinez@innn.edu.mx (I.E. Martínez-Juárez).

http://dx.doi.org/10.1016/j.yebeh.2016.04.047
1525-5050/

Despite VPA's acceptance as the first-line treatment for JME, the most appropriate VPA dose in patients with JME has not yet been established. A satisfactory response to a low dose of VPA (400–500 mg per day) can occur, achieving complete freedom from GTC and absence seizures but incomplete control of myoclonic seizures [21,22]. No significant differences in seizure frequency were observed when a daily dose of 1000 mg of VPA was compared with a daily dose of 2000 mg [23,24]; furthermore, increasing doses of VPA until side effects appeared did not appear to be very efficient [25].

The question that inspired our research was: what would be the appropriate dose and/or blood levels for VPA therapy in patients with JME? In an effort to answer this question, we compared seizure freedom between patients with JME taking a low dose of VPA with that between patients with JME taking a high dose of VPA. We also compared seizure freedom in patients with low VPA blood levels versus that in patients with high VPA blood levels.

2. Methods

2.1. Subject selection

We obtained clinical data from medical records of patients with JME who had been admitted to the epilepsy and genetic clinics of the National Institute of Neurology and Neurosurgery "MVS" from 2009 to 2012. Selected patients had to be taking VPA monotherapy for a minimum period of one year. The study was approved by the Institute's Research and Ethics Committees.

2.2. Data collection

Diagnosis of JME was performed using the criteria established by the International Genetic Epilepsy Studies Consortium (GENESS) following the ILAE 1989 commission [26]. We included medical records that had the following variables: VPA dose, blood levels, and length of time taking VPA; if any of these variables were missing, records were excluded. The last taken dose of VPA was recorded, and the patient must have been on that dose for at least one year of monitoring. The dose was classified as either low (≤1000 mg) or high (>1000 mg) for analysis. Valproate blood levels corresponded to the levels achieved with the last dose of VPA recorded in the patient's medical records. Valproate blood levels were then divided into ≤50 mcg/dl and >50 mcg/dl for analysis.

Other clinical variables were also documented, such as the following: current age, age at epilepsy onset, weight, gender, seizure types (isolated presence of myoclonias or their presence in combination with GTC, absence, and astatic seizures), JME subsyndrome, seizure freedom or poor control, electroencephalogram (EEG) findings, queries about family history of epilepsy, perinatal history, history of febrile seizures, history of moderate-to-severe head trauma, history of psychiatric disease prior to onset of epilepsy, previously used antiepileptic drugs (AEDs), relapses due to poor adherence, trigger factors, neuroimaging studies such as brain computed tomography (CT) or magnetic resonance imaging (MRI), presence of thyroid disease, and use of antidepressants.

Family history of epilepsy was documented in first-, second-, or third-degree relatives. Abnormal history of perinatal disorders was considered present when data included problems in pregnancy, fetal distress, neonatal hypoxia, or jaundice. Febrile seizures were considered present when seizures associated with hyperthermia occurred between 6 months and 6 years of age.

Electroencephalogram records were classified as the following: 1. normal: normal background, without epileptiform activity, asymmetries, or dysfunction; 2. abnormal typical: generalized and bilateral symmetrical and synchronous polyspike 4- to 6-Hz polyspike-wave complexes, and/or 3- to 4-Hz spike-and-slow wave complexes; and 3. abnormal atypical: EEG with focal discharges (spikes or sharp waves), asymmetries, and focal or generalized dysfunction as described by Betting et al. [27]. For analysis purposes, both typical and atypical findings were considered to be abnormal. The subsyndromes of JME were classified as previously described by Martínez-Juárez et al. [28].

"Persistent seizures" were defined as the presence of any seizure type (including absences, myoclonias, astatic, and/or GTC) in the last year, whereas "seizure-free" was defined as a lack of any seizure types for one year according to the ILAE criteria for seizure freedom [29].

Antiepileptic drug intake prior to the use of VPA was recorded; the previous use of benzodiazepines, LTG, PB, LEV, and TPM was considered appropriate. However, the previous use of phenytoin (PHT) or carbamazepine (CBZ) was considered to be inappropriate. Relapses from poor adherence were recorded. Triggers were also obtained for the purpose of documenting seizure relapses associated with sleep deprivation, stress, fatigue, alcohol, menstruation, photic stimulation, and fasting.

Because this was a retrospective study, some clinical data were missing from patients' records; missing or unknown data are described in the tables but were excluded when comparison analysis was performed.

2.3. Statistical analysis

The data were entered into a database for analysis. All calculations were performed with SPSSv17. Descriptive statistics used percentages and means for categorical and numeric variables, respectively. Comparisons between groups were performed using univariate analysis; a chi-square or Fisher's exact test were used for nominal variables, while Student's *t*-test or the Mann–Whitney U test were used for numeric variables.

3. Results

We reviewed 201 medical records of patients diagnosed with JME; 103 patients were on VPA monotherapy with at least one year of follow-up. Patients' seizure frequency was recorded together with VPA daily doses and VPA blood levels. We excluded 98 patients: six were on another monotherapy; 31 had incomplete data; 36 were on polytherapy with VPA; and 25 did not meet the criteria for JME, as they had other GGE.

3.1. Clinical characteristics

Among the patients, 56 (54.4%) were female, with an average current age of 28.4 ± 7.4 years (range: 16–50). The mean age of epilepsy onset was 13.6 ± 2.9 years (range: 6–23). Eighty-six patients (83.4%) belonged to the subsyndrome of classical JME. Ten (9.7%) patients had JME with astatic seizures, while seven (6.7%) patients had childhood absence that evolved to JME during adolescence.

The average time of use of VPA was 7.7 ± 6.6 years (range: 1–30). Valproate was the first drug used in 40 patients (40.8%), the second drug in 34 patients (33%), the third in 17 (16.5%), the fourth in nine (8.7%), and the sixth drug in one (1%). Sixty patients (58.3%) had used an AED that aggravated seizures before taking VPA. Twenty-two (21.35%) patients had a history of perinatal complications, while 77 (79.3%) patients denied any history of perinatal complications and four (4.1%) patients said that they did not know. Four (3.9%) patients had a history of febrile seizures during infancy and childhood, while 86 (88.58%) patients denied it and 13 (13.3%) did not provide an answer. Family history of epilepsy was present in 56 (54.4%) patients. Of these 56 patients, 31 (30.1%) had a first-degree relative with a history of epilepsy, 16 (15.5%) had a second-degree relative, and nine (8.7%) a third-degree relative with a history of epilepsy.