Journal of Epilepsy and Clinical Neurophysiology

J Epilepsy Clin Neurophysiol 2011;17(4):148-153

Effectiveness of the Use of an Omega 3 and Omega 6 Combination (Equazen™) in Paediatric Patients with Refractory Epilepsy

Eduardo Javier Barragán-Pérez[a], Irene Heredia-Barragán[b], Rosana Huerta-Albarran[b]

Federico Gómez Children's Hospital of Mexico – HIMFG

ABSTRACT

Introduction: Epilepsy is considered a health problem. 85% of patients are satisfactorily controlled with antiepileptic drugs (AEDs) and 15% have refractory seizures. The combination of omega 3 and omega 6 fatty acids (Equazen™) can contribute to changes in ionic currents and to stabilization of neurotransmitter's function resulting in cell membrane equilibrium. These changes lead to potential seizure control. **Objective:** To compare efficacy and safety in the treatment of refractory epilepsy with a supplement combining EPA, DHA (omega 3 fatty acids) and GLA (omega 6 fatty acids). **Methods:** We reviewed patients from the Neurology Department of the Children's Hospital of Mexico who have refractory epilepsy, evaluating clinical characteristics of seizures, number of seizures and AEDs. 792 mg of EPA, DHA and GLA per day (6 capsules of Equazen™) were administrated for four weeks in order to assess the frequency of seizures as well as tolerability and probable side effects. **Results:** The study was conducted with a total of 13 patients with follow-up four weeks after the start of supplementation. We obtained a satisfactory clinical response with ≥ 80% decrease in the daily number of seizures in more than 60% of patient. The mean of number of seizures over all patients was reduced significantly from 26.61±37.2 to 5.92 daily. In addition a significant improvement in the neurocognitive capacity was observedin all patients. **Conclusion:** The co-adjuvant supplementation with Equazen™ may result in a reduction of the number of seizures in refractory epilepsy having in addition significant impact on neurocognitive aspects. To enhance the quality of life of epileptic patient supplementation with a specific combination of EPA, DHA and GLA should be reconsidered.

Keywords: refractory epilepsy; omega 3, omega 6 fatty acids.

RESUMO

Eficácia do uso de uma combinação de ômega 3 com ômega 6 (Equazen™) em pacientes pediátricos com epilepsia refratária

Introdução: epilepsia é considerada um problema de saúde em que 85% dos pacientes são satisfatoriamente controlados com drogas antiepilépticas (DAE) e 15% tem crises refratárias. A combinação de ácidos graxos ômega 3 e ômega 6 (Equazen™) pode contribui em mudanças em correntes iônicas e estabilização de neurotransmissores, resultando em equilíbrio da membrana celular. Estas mudanças levam a potencial controle de crises. **Objetivo:** comparar a eficácia e segurança suplementos combinando EPA, DHA (ácidos graxos ômega 3) e GLA (ácidos graxos ômega 6) no tratamento da epilepsia refrataria. Métodos: crianças com epilepsia refratária do Departamento de Neurologia do Hospital Infantil do México tiveram avaliadas as características de suas crises, frequência e numero de DAEs. EPA, DHA e GLA (6 capsulas de Equazem – 729mg) foram administrados em um período de 4 semanas, sendo acessados tolerabilidade, efeitos colaterais e frequência de crises. **Resultados:** 13 pacientes foram avaliados por 4 semanas após o início da suplementação. Um controle clínico satisfatório (redução de 80% ou mais das crises) foi obtido em 60% dos pacientes (26.61±37.2 crises para 5.92 crises ao dia), além de significativa melhora em sua capacidade neurocognitiva. **Conclusão:** a suplementação de Equazen pode determinar redução no número de crises em epilepsia refratária e determinar melhora em parâmetros neurocognitivos. O uso da combinação EPA, DHA, GLA deveria ser reconsiderado neste cenário.

Unitermos: epilepsia refratária; ácidos graxos ômega 3, ômega 6.

[a] Paediatric Neurologist. Attached to Paediatric Neurology Department, HIMFG. Profesor of Neuropediatrics, UNAM.
[b] Paediatric Neurologist. Federico Gómez Children's Hospital of Mexico (HIMFG).
Received Oct. 25, 2011; accepted Dec. 07, 2011.

INTRODUCTION

Epilepsy is considered to be the most common paroxysmal event in childhood and is second only to mental retardation among neurological diseases[1].

About 80-85% of the epilepsy patients are satisfactorily managed and treated with the classic antiepileptic drugs (AED) while 15-20% requires an alternative pharmacological option or even surgical procedures[2].

As epilepsy is one of the main causes for attending our institution (65% of all neurology consultations in the hospital) and despite the many treatments available, there remain 15% of epileptic patients who do not respond to drug therapies. Therefore it is important to look for alternative treatments, especially for those, which can sustain seizure control thereby reducing the secondary complications like somnolence or cognitive decline. They may also be expected to offer economically more accessible options and have an impact on quality of life.

According to some authors, up to 30% of epilepsy cases have intractable seizures or adverse reactions to the medication, while other authors consider that only 5% to 10% cannot be controlled with the known drugs and these are categorized as difficult-to-control or refractory epilepsies[2].

Refractory epilepsy (RE) is defined as a lack of seizure control, despite the correct diagnosis being made and the use of at least two antiepileptic drugs indicated for epilepsy at the maximum tolerated doses, with therapeutic serum levels being maintained for a minimum of six months[3].

The specific combination of the fatty acids EPA, DHA (belonging to omega 3 polyunsaturated fatty acids) and GLA (omega 6 polyunsaturated fatty acids) may change the ion currents of the neurons, which sustain the normal neurotransmitters function for the synaptic transmission. The increased concentration of EPA, DHA and GLA in the central nervous system (CNS) may stimulate and sustain myelinisation resulting in stabilization of the cell membrane and possibly leading to control of epileptic seizures[4].

The progression of epilepsy until it becomes a refractory process may be caused by changes in the cerebral circuits that are reorganized after the initial lesion or after status epilepticus or/and by the individual's genetic anomalies and variations (mutations and polymorphisms), which influence how the individual reacts to aggression and thus affects the development of the acquired symptomatic epilepsy. It is not to ignore that this clearly multifactorial condition can be related even to other aspects[17].

One of the most important risk factors for developing refractory epilepsy is determined by the type of epilepsy. Patients with partial complex seizures have a higher rate of seizure recurrence than those who have generalized tonic-clonic seizures. Numerous studies have shown that symptomatic partial epilepsies are associated with a higher risk of resistance to treatment with antiepileptic drugs and seizure recurrence after an initial episode. On the other hand, the group of seizure-free patients is much larger among those with idiopathic generalized epilepsy than those with cryptogenic and symptomatic partial seizures[20].

Since there remain cases of refractory epilepsy, regulating the co-factors by the administration of food supplements, such as a specific combination of omega 3 and 6 fatty acids (Equazen™), has now been proposed. Apparently the supplement acts as a stabilizer of the post-synaptic membrane, which may sustain the treatment management with the different antiepileptic drugs[12].

Although only a small number of patients suffer from difficult-to-control seizures, the socio-economic, medical and family consequences are very significant. These include adverse reactions to the multiple drug therapy, abnormal behaviours, long periods of hospitalization, multiple infectious complications and school failure. There are clinical and electroencephalographic factors which are associated with refractory epilepsy[8].

METHOD

The aim of our study is to compare the clinical response to treatment of refractory epilepsy by administration of a specific combination of omega 3 and omega 6 fatty acid (Equazen™). It is a prospective, longitudinal pilot clinical trial. All patients (male and female) aged between 4 and 16 years attending the out-patients clinic of the Neurology Department, Children's Hospital of Mexico "Dr. Federico Gómez", and suffering from refractory epilepsy, regardless of the type of epilepsy (partial or generalized), were considered for inclusion in the trial. Patients who had previously been treated with a ketogenic diet or with omega 3 and omega 6 fatty acid supplements, surgery for epilepsy, patients with third-grade malnutrition, epilepsy of degenerative origin and systemic disease preventing administration of the diet were excluded.

The clinical characteristics of the epileptic seizures confirming the presence of refractory disease were assessed, their clinical presentation being evaluated by a neurologist in the outpatients department. The clinical identification of these characteristics was correlated with the electroencephalogram, although this was not the determining factor when classifying the site affected. The omega 3 and 6 fatty acid supplement (Equazen™, Vifor Pharma) was added at a dose of six capsules a day (558 mg EPA, 174mg DHA and 60mg GLA) for four weeks. The patients' neuroimaging results as well as the drug treatment they were taking were analysed.

The patients were followed up in the Neurology Department by means of a seizure diary to find out the

number and characteristics of their seizures. A baseline conventional electro-encephalogram was taken and followed up after four weeks. Clinical assessment was also conducted two and four weeks after patients started the diet.

The Clinical Global Impression (CGI) severity scale was completed by the parents and the investigator. The patients for whom a paediatric and neurological clinical history as well as a general physical and neurological examination were carried out were assessed during the period from September 2009 to June 2010.

STATISTICAL ANALYSIS

The SPSS for Windows statistics package was used. Descriptive statistical analysis was performed to analyse the data distribution by means of frequency tables, measures of central tendency and scatter, histograms, pie charts and normal curves. The results for the different variables were analysed by non-parametric hypothesis testing for independent samples to compare two means (Mann-Whitney U-test or Wilcoxon). Non-parametric one-way ANOVA for paired groups was also used to compare more than two means (X2 Friedman and Kendall's). In all the results, the statistical significance was set at $\alpha=0.05$ with 95% confidence intervals.

RESULTS

A total of 13 patients with a diagnosis of refractory epilepsy, who fulfilled the inclusion criteria, were included in the trial. Seven were male (53.84%) and six female (46.15%). Their mean age was 8.46±3.86 years and the age group distribution was as follows: pre-school 30.76% school age 30.76%, adolescent 38.46%. The distribution of the number of antiepileptic drugs used was as follows: two antiepileptic drugs in 38.46%, three drugs in 53.84% and finally four antiepileptic drugs were used in only one patient (7.69%).

In terms of the type of seizures, 61.43% were partial and 38.46% were generalized.

We observed a significant improvement in the neuro-cognitive capacity of all the patients and in the patients' quality of life, assessed by the CGI. The improvement was not directly related to the decreased frequency of seizures. A decrease of more than 4 points was observed.

During the study each patient received 792 grams daily of omega 3 and omega 6 for one month. Every week a meeting with the family and the patient was arranged in order to check the mean number of seizures per day recorded in the patient's diary.

At basis (without supplementation) a mean number of 26.61 seizures was obtained. This mean number of seizures decreased to 11.30 by the first week, to 10.76 in the second week, to 8.76 in the third week and finally to 5.92 in the fourth week (see Table 1). In terms of the mean, a statistically significant decrease of more than 75% in the daily number of seizures was therefore found after 4 weeks of supplementation compared to the base before supplementation ($p<0.05$).

The Figure 1 shows the decrease in the weekly number of seizures per patient before and after one to 4 weeks of supplementation with the omega 3 and omega 6 combination.

Overall a decrease of the daily seizures number was observed after the first week as also to the 4 week compared to the number before supplementation. Only patient number 5 did not show any decrease. Patient number 11 had a slightly increase of the daily epileptic seziures.

The Figure 2 shows the weekly number of seizures from week 2 to 4 after the start of supplementation.

The results for the different variables were analysed by means of non-parametric hypothesis testing for independent samples to compare two means (Wilcoxon). Significant differences with a two-tailed test were found) by comparing the daily mean seizures numbers after week 1 (11.30) and week 4 (5.92) (p=0.008). No increase in the number of seizures was found in any patient. The number of daily seizures decreased in 8 patient and remained unchanged in 5. Significant differences of the daily seizures number were also found when comparing week 1 (11.30) and week 3 (8.76) (p=0.032), but not between week 1 and week 2 (10.76; p=0.623), as shown in Table 1.

Table 1. Descriptive statistics of number of seizures per day before and after administration of Equazen™

	NC Before supplementation	NC after 1 supplementation week	NC after 2 supplementation week	NC after 3 supplementation week	NC after 4 supplementation week
Mean	26.61	11.30	10.76	8.76	5.92
Median	21.00	8.00	7.00	5.00	3.00
Mode	21.00	1.00	7.00	1.00	3.00
Minimum	1	0	1	1	0
Maximum	140	51	61	46	39

NC= number of epileptic crisis.

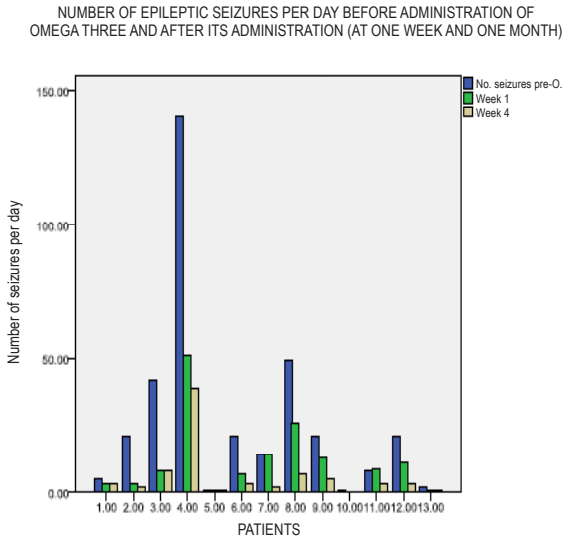

Figure 1. Number of seizures per day, before and after (week 1 and 4) the administration of Equazen™.

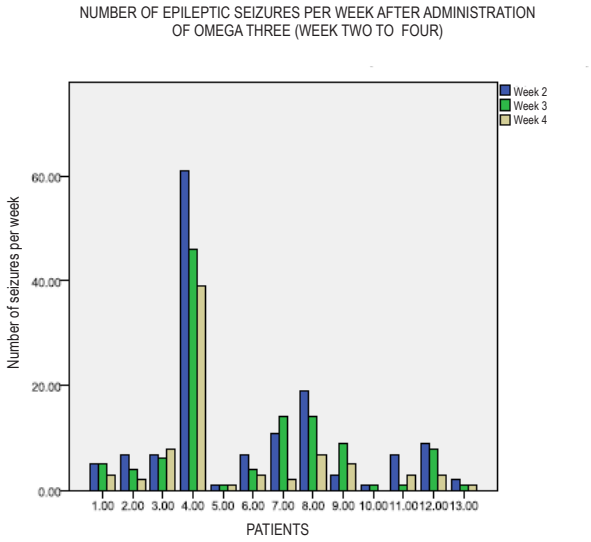

Figure 2. Number of epileptic seizures per week after administration of omega 3.

Table 2. Non-parametric one-way ANOVA comparing the number of seizures before supplementation with week 1 to 4 Afterequazen™ supplementation.

Week		Sum of Squares	df	Mean Square	F	Sig.
Week 4	Between Groups	1243.673	8	155.459	118.445	.000
	Within Groups	5.250	4	1.313		
	Total	1248.923	12			
Week 3	Between Groups	1729.558	8	216.195	41.676	.001
	Within Groups	20.750	4	5.188		
	Total	1750.308	12			
Week 2	Between Groups	2993.308	8	374.183	78.771	.000
	Within Groups	19.000	4	4.750		
	Total	3012.308	12			
Week 1	Between Groups	2255.269	8	281.909	18.952	.006
	Within Groups	59.500	4	14.875		
	Total	2314.769	12			

Non-parametric one-way ANOVA for paired groups was also used. In all the results the statistical significance level was set at $\alpha=0.05$ with 95% confidence intervals.

When ANOVA was used, all the tests were statistically significant but our hypothesis was only corroborated when comparing the number of seizures before administration of the omega 3 and 6 supplementation and the second and fourth weeks, not in the third and first weeks (taking into account the F-values in the tables corresponding to degrees of freedom in our study, $F=43.39$ as shown in Table 2 above).

DISCUSSION

Epilepsy is recognized worldwide as a public health problem, with a prevalence ranging from 1.5 to 10.8 per 1000 people. This has major repercussions for working and social life as well as health, exacerbating socio-economic conditions (which are already unstable in Mexico), given the daily struggle to maintain the cost of antiepileptic drugs.

The fact that only 80-85% of patients with epilepsy are satisfactorily controlled with antiepileptic drugs (AED) forces us to search for more treatment options for the remaining percentage (10-15%) who meet the criteria for refractory epilepsy.

The group of patients studied in the present trial was heterogeneous, with characteristics and criteria consistent with the diagnosis of refractory epilepsy. Given the study objective, the efficacy of the fatty acids omega 3 and omega 6 (Equazen™) as additive therapy for refractory epilepsy is demonstrated in the paediatric population of the Children's Hospital of Mexico.

The most interesting finding from our study, which was not currently the first study objective, is the presence of an improvement in 100% of patients in their neurocognitive capacity and their quality of life, assessed by the CGI. This was not found to be related to the effect of the fatty acids omega 3 and omega 6 in terms of ≥80% decrease in the daily number of seizures in 60% of patients. This effect was regarded as another independent effect on neurocognitive capacity, which suggests that the usefulness of an omega 3 and omega 6 combination as a co-adjuvant supplement should also be reconsidered in the overall improvement of epilepsy patients.

CONCLUSIONS

In this study our hypothesis that the combination of EPA, DHA and GLA reduces the frequency of the number of seizures in patients with refractory epilepsy is proved. While the statistical tests (Wilcoxon and ANOVA) vary in significance on this point before four weeks, they both agree that by week 4 there is a decrease associated with administration of the supplementation. This might be explained by the time the supplement needs to be administered in order to reach adequate therapeutic levels.

According to our study, the response to Equazen™ as additive treatment to antiepileptic drugs reduces the seizure frequency by 80% in more than 60% of the total number of patients studied.

Its impact on neurocognitive aspects in 100% of patients, observed at the same time, gives cause to reconsider its usefulness in the comprehensive improvement of epileptic patients.

ACKNOWLEDGEMENT

Vifor Pharma provided the supplement for this study. The staff of the neurology department, HIM, is acknowledged for supporting the study.

REFERENCES

1. Schuele SU and Lüders HO.Intractable Epilepsy: management and therapeutic alternatives. Lancet Neurol 2008; 7:514-24.
2. Raspall-Chaure M. The Medical Management of the epilepsies in children: conceptual and practical considerations. Lancet Neurol 2008; 7:57-69.
3. ILAE'S Centenary Congress in Budapest, Hungary, June 28th to July 2nd, 2009.
4. Panico LR et al. The electroencephalographic evolution of a group of patients on a ketonic diet. Rev Neurol 2000; 30;8-15.
5. Fisher RS et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005; 46(4): 470-2.
6. Eriksson KJ and Koivikko MJ. Prevalence, Classification and Severity of Epilepsy and Epileptic Syndromes in children. Epilepsia 1997; 38(12):1275-82.
7. Guidelines for epidemiological studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 1993; 34:592-596.
8. Aicardi J. Epilepsy in children. 2nd ed. New York: Raven Press; 1994. p. 194-9.
9. Vacca G et al.. Definición de medicamento genérico: un fin o un medio? Análisis de la regulación en 14 países de la región de las americas. Rev Panam Salud Pública 2006; 20(5):314-23.
10. González Salazar M. Dieta cetogénica como tratamiento de adición en pacientes con epilepsia refractaria en el Hospital Infantil de México. Tesis de Especialidad en Nutrición Clínica Pediátrica. 2005.
11. Walberg Ekvall S, Iannaccone S. Pediatric Nutrition. EUA; 1995. Cap. 8: Epilepsy. p. 100.
12. Estimated Average Requirements for Groups Food and Nutrition Board, Institute of Medicine, National Academies. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids; 2005. p. 365-378.
13. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985; 39(Suppl 1): 5-41.
14. Ruíz GM et al. Dieta cetogénica. Una alternativa terapéutica para la epilepsia refractaria. Nutr Clin 2000; 3(1):9-14.
15. Fuehrlein B et al. Differential metabolic effects of saturated versus polyunsaturated fats in ketogenic diets. J Clin Endocrinol Metab 2007; 89(4):1641-45.
16. Kwan P and Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342(5):314-9.
17. Téllez-Zenteno JF and Wiebe S. Long-term seizure and psychosocial outcomes of epilepsy surgery. Curr Treat Options Neurol 2008; 10(4):253-9
18. Kutsy RL. Focal extratemporal epilepsy: clinical features, EEG patterns, and surgical approach. J Neurol Sci 1999; 166(1):1-15.
19. Semah Fet al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998; 51(5):1256-62.
20. Manford M, Hart YM, Sander JW, Shorvon SD. National General Practice Study of Epilepsy (NGPSE): partial seizure patterns in a general population. Neurology 1992; 42:1911-7.
21. Jan MM and Girvin JP. Seizure semiology: value in identifying seizure origin. Can J Neurol Sci 2008; 35(1):22-30.
22. Bancaud Jand Talairach J. Clinical semiology of frontal lobe seizures. Adv Neurol 1992; 57:3-58.
23. Swartz BE. Unusual seizure types. Semin Neurol 1995;15(2):151-7.
24. Taylor I et al. Occipital epilepsies: identification of specific and newly recognized syndromes. Brain 2003; 126(Pt 4):753-69.
25. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989; 30(4): 389-99.
26. Salanova V et al. Parietal lobe epilepsy. Clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988. Brain 1995; 118(Pt 3):607-27.
27. Lefkopoulos A et al. Magnetic resonance imaging in 120 patients with intractable partial seizures: a preoperative assessment. Neuroradiology 2005; 47(5):352-61.
28. Cakirer S et al. MR imaging in epilepsy that is refractory to medical therapy. Eur Radiol 2002;12(3):549-58.
29. Golbitz P. (Ed.). Soya & oilseed bluebook. Massachusetts; 2000.
30. Sprecher H. Long chain fatty acid metabolism. In: U. Bracco and R.J. Deckelbaum, Editors, Polyunsaturated Fatty Acids in Human Nutrition, Raven Press, New York; 1992. p. 13-24.
31. Baur Let al. The fatty acid composition of skeletal muscle membrane phospholipid: its relationship with the type of feeding and plasma glucose levels in young children. Metabolism 1998; 47(1):106-12.
32. Forsgren L et al. The epidemiology of epilepsy in Europe –a systematic review. Eur J Neurol 2005; 12(4):245-53.

33. Nieto-Barrera M. Neuroepidemiology of epilepsies. An Esp Pediatr 1988; 29(Suppl 33):59-63.

34. Ochoa-Sangrador C and Palencia Luaces R. Study of the prevalence of epilepsy among schoolchildren in Valladolid, Spain. Epilepsia 1991; 32(6):791-7.

35. López-Pisón J et al. Casuística de epilepsias idiopáticas y criptogénicas en una unidad de neuropediatría de referencia regional. Rev Neurol 2000; 31:733-8.

36. Durá-Travé T and Yoldi-Petri ME. Epilepsy and epileptic syndromes among primary school children (6-12 years). An Pediatr (Barc) 2007; 66(1):11-6.

37. Saiz-Díaz R. Antiepilépticos: aportación de los nuevos fármacos. Inf Ter Sist Nac Salud 2004; 28:33-40.

38. Kotsopoulos IA et al. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. Epilepsia 2002; 43(11):1402-9.

39. Cockerell OC et al. Remission of epilepsy: results from the National General Practice Study of Epilepsy. Lancet 1995; 346(8968):140-4.

40. Lindsten Het al. Remission of seizures in a population-based adult cohort with a newly diagnosed unprovoked epileptic seizure. Epilepsia 2001; 42(8):1025-30.

Address for correspondence:
Eduardo Barragán Pérez
Av. Cuauhtémoc, 882 – Col Narvarte Poniente
CP 03020, Delegación Benito Juárez, México DF, Mexico
E-mail: <neurodoc@prodigy.net.mx>