RESEARCH ARTICLE

USE OF CLONAZEPAM AND AVOIDANCE OF SLEEP DEPRIVATION IN THE TREATMENT OF JUVENILE MYOCLONIC EPILEPSY

Rafiei S.M. MD

Associate Professor of Child Neurology, Division of Neurology, Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz ,Iran

Corresponding Author: Rafiei S.M. MD, Namazi Hosptial,Shiraz, Iran
email: rafieim@sums.ac.ir

Received: 06-May-2009
Last Revised: 04-Nov-2009
Accepted: 04-Nov-2009

Abstract

Objectives

Juvenile Myoclonic Epilepsy(J.M.E.) needs life-long anti-epileptic drug (AED) treatment. Of various drugs tried in this condition, valproate effectively treats all types of seizures seen in J.M.E.

Among valproate side effects, neural tube defects (NTD) in the offspring, is a deterring factor in its use in childbearing period. To avoid NTD, most authorities advise on switching to AED drug before conception.As well, the effects of valproate on male fertility is feared of.

Clonazepam controls only the myoclonic jerks, leaving the patients unprotected and susceptible to generalized seizures, which mostly occur in the morning after sleep deprivation. Sleep deprivation is the most prevalent precipitating factor for generalized seizures in these patients.

Materials &Methods

Between Jan 2003 & April 2008, 15 newly diagnosed JME patients (9 girls, 6 boys), were given clonazepam (1.0-4.0 mg) at bedtime, and were compared to 16 patients on valproate treatment. All were advised to avoid sleep deprivation.

Results

This study showed, all patients in the clonazepam group, (100 %) had full control of their myoclonic jerks; 4(26.6%) had breakthrough episodes of generalized seizures, provoked by sleep deprivation; the rest (11,73.4 %), were in full remission of their myoclonic and generalized seizures. In control group, 2(12.5 %), had episodes of breakthrough, sleep-deprived, generalized seizures;the rest(14, 87.5%) were in remission. Statistically, there was no significance between the results in both groups.

Clonazepam side effects were limited to mild to moderate drowsiness in the morning, eliminated by giving the dose earlier at night.

Conclusion

The study suggests that if J.M.E. patients avoid sleep deprivation, they can be treated with clonazepam alone to avoid side effects of valproate.

Keywords: Juvenile Myoclonic Epilepsy ,Clonazepam, Sodium valproate (Valproic Acid), Sleep precations, Sleep Deprivation

Introduction

Juvenile Myoclonic Epilepsy (of Janz) is a well known epileptic syndrome for its propensity to affect preadolescent and adolescent age groups (1, 2, 3). Although idiopathic and easily controlled by anti-epileptic drugs, it relapses whenever the drug is withdrawn; hence a life-long treatment is usually is needed, which exposes the

patients to potential side effects of the drugs, especially in female patients (4, 5, 6, 7, 8, 9). Of various AED's used, Valproate ranks first as the drug of choice, because it easily controls all three seizure types (genralized, absence and myoclonic) seen in J.M.E(3, 5, 6). However it has potential side effects including, GI disturbances, pancreatitis, endocrine, and teratogenic and cognitive side effects on the offspring. Neural tube defects, mainly meylomeningocele, are seen in as high as 6% of offsprings of mothers on valproate during pregnancy, especially when on doses exceeding 1000mg/day (4, 7, 8, 10, 11); other effects include: midline defects such as hypospadias, partial agenesis of corpus callosum, ventricular septal defects; as well the effects of Valproate on infant neurodevelopment are well feared of (9, 12). There are concerns about the effects of valproate on male fertility (9). Hence many authorities advise on switching valproate to a safer drug before conception, like topiramate or lamotrigine, or discontinue valproate before conception and cautiously give anti-myoclonic AED's during pregnancy for those with predominantly myoclonic episodes (3, 6, 9).

Clonazepam, a long-acting benzodiazepine, controls the myoclonic jerks, but leaves the patient unprotected for the generalized seizures, which ususally occur after a period of sleep deprivation, (14, 15). The generalized seizures are usually heralded by myoclonic jerks.

Sleep deprivation is a potent precipitating factor for generalized seizures in these patients, usually which occur early in the morning after a period of sleep deprivation for exam tests, wedding ceremonies, or Ramadan fasting.

The purpose of study was to see if a combination of clonazepam and total avoidance of sleep deprivation could prevent the occurrence of generalized seizure episodes in JME, hence obviate the need to use valproate.

Materials & Methods

Between January 2003 and April 2008, among patients seen in the author's private clinic, fifteen patients (9 girls, 6 boys), clinically diagnosed as J.M.E. were randomly selected as the study group. Evaluation consisted of history, physical and neurological examination, and a conventional EEG performed by standard 10-20 system, using a Nyhon-Cohden EEG (Japan), or Neuroscan LT (USA) machine. However, EEG was not used as a criterion for patients' selection. History for early morning myoclonic jerks, followed by generalized seizure, was the basis for the diagnosis of J.M.E. Sixteen other patients (10 girls and 6 boys) on sodium valproate treatment, served as control group for the period of study. Written consents were obtained from the patients in study group.

Patients in study group were given titrating doses of clonazepam, 1-4 mg doses, as the sole anti-epileptic drug, at night 1 hour before retiring, aimimg at full control of myoclonic jerks. Control patients received sodium valproate, 15-20 mg/kg/day in 2 or 3 divided doses, to be taken after meals.

Patients in both groups were advised to avoid sleep deprivation and interruption, and were monitored for AED side effects. Those in study group who had breakthrough seizures were switched to sodium valprate. Patients in study group had periodic tests of complete blood count (CBC); Valproate group underwent periodic assessment of CBC, platelet count and liver function tests. Fisher's Exact Test was used for statistical analysis. An English language literature search was made.

Results

Age of the patiests ranged from 10 years to 23 years. Girls outnumbered in both groups. All patients had normal neurological examinations. None of the female patients in both groups were married. Most had normal awake EEG's (only 4 abnormal EEG's, 12.9%) in both groups. During period of study and follow up, of patients in study group, 11 patients (73.4 %), experienced full remission (no generalized seizure). The rest (4, 26.6 %) had breakthrough generalized seizures at early morning, always after a period of interrupted or incomplete sleep. They were switched to valproate regimen for the rest of the study period, with no further breakthrough seizures. In the control group, 2(12.5%) had breakthrough early morning generalized seizures, in all after sleep deprivation;the rest (14, 87.5%), had full remission. None of the subjects in study or control group consumed alcohol.

In both groups myoclonic jerks were fully controlled with either clonazepam or valproate.

Side effects of clonazepam were limited to early morning

drowsiness in study group in all subjects when the dose was titrated up to 4 mg/day. Drowsiness lessened or subsided as the dose was given earlier at night and as the regimen continued. None of the patients on clonazepam had any change in hemogram.

Side effects of sodium valproate in control group and those switched to it from study group were: abdominal pain in10 patients, obesity in 4, hair loss in 6, and menstrual irregularities in 3 patients. None of the patients on valproate had changes in hemogram or liver function tests during the period of study. Statistically, there were no significances between the two groups in control of generalized seizures (P-value=0.394)

Discussion

J.M.E is the only idiopathic seizure disorder in which anti-epileptic drugs must be continued life –long (1, 2, 3), although myoclonic jerks may subside later in life (19). Valproate controls all three types of seizures, but exposes the patient to various side effects, like polycystic ovary syndrome, obesity, hair loss, and decreased sperm count in the male, and neural tube defects and neuro-developmental delay in the offspring (5-12). Various other drugs have been tried, but each has its caveat, or does not cover all aspects of the disease. For example, carbamazepine controls the GTCS component, but may exacerbate absence and myoclonic seizures(3). Lamotrigine, while controlling absence and generalized seizures(13), may aggravate the myoclonic component, especially at higher concentrations(16,17), and has been associated with non-syndromic cleft palate in the offspring(22). Levetiracetam is recently another choice for treatment of JME, and although it may become soon the drug of first choice, but it is expensive in Iran(18, 23, 24). Clonazepam readily controls the myoclonus, and sometimes the absence, but is relatively ineffective on GTCS's (3, 6,10,11).

Since most of the generalized seizures in these patients is provoked by sleep deprivation, its avoidance per se could potentially prevent generalized seizures, mostly seen at early morning.

A literature search did not yield any comparable study. Clonazepam per se has not been yet used in the treatment of JME for the fear of masking the myoclonias which is a warning sign for these patients to take rest and use a rapid-acting benzodiazepine before the generalized seizure sets in (1, 2, 3).

This study shows that the potential side effects of valproic acid could be avoided by a combination of clonazepam and strict avoidance of sleep deprivation.

The main side effects of clonazepam are drowsiness and excessive oro-tracheal secretions (14,15). Drowsiness, seen in the study group early in the morning, was eliminated by giving the appropriate doses several hours before sleep. No other side effects were seen. Regular CBC done showed no hematologic derangement. On the other hand patients on valproate showed various side effects. No particular pregnancy risks has been found in association with clonazepam (14), except when given with other AED's as polytherapy(10). Although the result of this study is not statistically siginificant regarding control of seizures (P value= 0.394), it seems prudent to advise cooperative and compliant J.M.E. patients to use clonazepam along with strict sleep precautions, life –long, to avoid valproic acid side effects. Sleep precaution is mandatory, especially during study years, wedding ceremonies, and during child nurturing periods, when sleep deprivation or interuption episodes are usual.

In conclusion, If used with strict sleep precautions, clonazepam can substitute sodium valprate, thus avoiding its potentially harmful side effects.

Acknowledgement

The atuthor is thankful to patients for cooperation and consent for the study.

Disclaimer

The author has nothing to disclaim.

Table 1. Comparrison of charachteristics of Study & Control Group

	Study Group	Control Group	P Value
Male	6 (40%)	6 (37.5%)	1
Female	9 (60%)	10 (62.5%)	
No Generalized Seizures	11 (73.4%)	14 (87.5%)	0.394
Generalized Seizures	4 (26.6%)	2 (12.5%)	

References

1. Kobayashi E, Zifkin BG, Anderman F, Anderman E; Juvenile Myoclonic Epilepsy. In:Engel J, Pedly T(eds): Epilepsy: A Comprehensive Textbook. 2nd ed. Philadelphia: Lippincott Williams & wilkins; 2008.P. 4713-4725.
2. Zifkin B, Anderman E, Anderma F. Mechanisms, Genetics, and Pathogenesis of Juvenile Myoclonic Epilepsy. Curr Opin Neurology 2005;18:147-153.
3. Loddenkemper T, Benbadis SR, Serratosa JM, Berkovic SF. Juvenile Myoclonic Epilepsy. In:Elaine Wyllie (eds): The Treatment of Epilepsy Principles and Practice. 4th ed. Philadelphia: Lippincott Williams & Willkins;2006. P.392-396.
4. Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB. Increased Rates of Major Malformations in Offsprings Exposed to valproate During Pregnancy. Neurology 2005;64:961-965.
5. Beydoune AA, Farrell K, Nasreddine WM. Valproate. In: Engel J, Pedly T(eds): Epilepsy: A Comprehensive Textbook. 2nd edition. Philadelphia: Lippincott Williams & wilkins;2008. P.3251-3271.
6. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006;47:1094-120.
7. Vajda FJ, O'Brien TJ, Hitchcock A, GrahamJ, Cook M, Lande C, et al. Critical Relationship Between Sodium Valproate Dose and Human Teratogrnicity:Result of the Australian Register of Anti-epileptic Drugs in Pregnancy. J Clin Neurosci 2004;11:854-8.
8. Duncan S. Teratogenesis of sodium valproate. Curr Opin Neurol 2007;20:175-180.
9. Ben-Menachem E, Schmitz B, Tomson T, Vajda FJ. Role of Valproate Across Age;Treatment of Epilepsy in Adults. Acta Neuol Scan 2006;114 (184 suppl):14-27.
10. Samren EB, van Duijn CM, Christiaens GC, Hofman A, Lindhout D. Antiepileptic drug regimens and major congenital malformations in the offspring. Ann Neurol 1999;46:739-746.
11. Torbjorn T, Battino D. Teratogenic effects of antiepileptic drugs. Seizure 2008; 17:166-171.
12. Nicolai J, Vles JSH, Aldenkamp AP Neurodevelopmental delay in children exposed to antiepileptic drugs in utero: A critical review directed at structural study-bias. 2008 Aug 15;271(1-2):1-14. Epub 2008 May 13.
13. Buchanan N. The use of lamotrigine in juvenile myoclonic epilepsy. Seizure 1996; 5: 149-51.
14. Schmidt D, Wilensky AJ. Benzodiazepines. In: Engel J, Pedly T(eds): Epilepsy: A Comprehensive Textbook, 2nd ed. Philadelphia: Lippincott Williams & wilkins; 2008. P.2971-2991.
15. Riss J, Cloyd J, Grates J, Collins S. Benzodiazepines in epilepsy: Pharmacology and Pharmacodynamics. Acta Neurol Scan 2008;118:69-86.
16. Guerrini R, Dravet C, Genton P, Belmonte A, Kaminska A, Dulac O. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia 1998;39:508-12.
17. Crespel A, Genton P, Berramdane M, Coubes P, C. Monicard C, Baldy-Moulinier M. Lamotrigine associated with exacerbation or de novo myoclonus in idiopathic generalized epilepsies. Neurology 2005; 65: 762-64.
18. Verrotti A, Manco R, di Marco G, Chiarelli F, Franzoni E. The treatment of juvenile myoclonic epilepsy. Expert Rev Neurother 2006; 6: 847-54.
19. Baykan B, Altindag AE, Bebek N, Ozturk A.Y, Aslantas B, Gurses C, et al. Myoclonic Seizures Subside in the Fourth Decade in Juvenile Myoclonic. Epilepsy Neurology 2008;70: 2123-2129.
20. Lande CM. Antiepileptic drugs in pregnancy and lactation.Australian Prescriber 2008 ;31:70-2.
21. Biton V, Bourgeois BF. Topiramate in patients with juvenile myoclonic epilepsy. Arch Neurol 2005;62(11):1705-1708.
22. Holmes LB, Baldwin EJ, Smith CR, Habecker E, Glassman L, Wong SL, Wyszynski DF. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008; 70:2152-2158.
23. Abou-khalil B. Levetiracetam in the treatment of epilepsy. Neuropsychiatric Disease and Treatment 2008; 4(8):507-523.
24. Auvin S. Treatment of Juvenile Myoclonic Epilepsy.CNS Neuroscience and therapeutics 2008; 14(3)227-233.