Cukurova Medical Journal

Araştırma Makalesi / Research Article

Valproic Acid: Does It Have an Antiarrhythmic Action?

Valproik Asit Aritmiye Yol Açar mı?

Osama Shukir Muhammed Amin[1], Ali Mahmood[2]

[1]Department of Neurology, Sulaimaniya General Teaching Hospital, Sulaimaniya city, Iraq..

[2] Department of Public Health, Iraqi Ministry of Health, Baghdad, Iraq.

Cukurova Medical Journal 2013; 38 (4): 592-600.

ABSTRACT

Purpose: The antiepileptic sodium valproate (valproic acid; VPA) is thought to possess an antiarrhythmic action. We aimed to explore whether this medication influences cardiac atrial ectopics or not.

Material and Methods: From December 1, 2009 to June 1, 2011, 80 consecutive patients who were newly diagnosed with cryptogenic generalized tonic-clonic seizures were enrolled in this prospective short-term longitudinal observational study, which was conducted at the Sulaimaniya General Teaching Hospital, Iraq. Forty patients were allocated to receive VPA and the rest (n=40) were given placebo. All patients underwent cardiac 24-hour Holter monitoring before and after one week of VPA or placebo administration. The minimum heart rate (MiHR) and maximum heart rate (MxHR) as well as the total number of atrial ectopics (TNAE) were evaluated.

Results: VPA significantly reduced the MiHR, MxHR, and the TNAE. In the placebo group, the reduction in the MiHR was statistically significant while the reduction in the MxHR and the TNAE were not. However, the reduction in the target parameters in the VPA-treated group did not demonstrate a dose-dependent effect. When both groups were evaluated head-to-head for the reduction in the MiHR before and after week of therapy, there was no statistically significant difference between them.

Conclusion: Sodium valproate therapy appears to be effective against atrial ectopic beats and may be used as an antiarrhythmic medication in patients who co-experience seizures and troublesome atrial ectopics.

Key Words: sodium valproate; Holter monitoring; atrial ectopic; seizure.

ÖZET

Amaç: Antiepileptik olan sodyum valproat (valproik asit: VPA) ın anti aritmik bir etkiye de sahip olduğu düşünülmektedir. Bu çalışmanın amacı VPA'ın ektopik kardiak aritmi tedavisi üzerine etkisinin olup olamadığını araştırmaktır.

Materyal-Metod: 1 Aralık 2009 ile 1 Haziran 2011 tarihlerini kapsayan çalışmamızda kriptojenik generalize tonik klonik nöbet tanısı almış 80 hasta prospektif bir çalışmayla gözlemlenmiştir. Bu çalışma Irak Sulaimaniya Genel Eğitim Hastenesinde yapılmıştır. Kırk hastaya VPA verilirken ve geri kalan 40 hastaya plasebo verildi. VPA uygulaması başlamadan 1 hafta öncesinden başlayarak ve 1 hafta sonrasına kadar tüm hastalar 24 saat boyunca kardiyak holter ile gözlemlenmiştir. Minumum kalp hızı oranı (MiHR) ve maksimum kalp hızı oranı (MxHR) ile total ektopik atrial aritmi sayıları (TNAE) değerlendirildi.

Bulgular: VPA nın MiRH, MxRH ve TNAE yi önemli derecede azalttığı görülmüştür. Plasebo grubunda; MiHR grubundaki azalma istatistiksel olarak anlamlı iken MxRH ve TNAE gruplarındaki azalma anlamlı değildi. Ancak VPA ile tedavi edilen grupta görülen azalma doza bağımlı bir etki oluşturmamıştır. Terapiden 1 hafta öncesinde ve sonrasında yapılan değerlendirmede iki grup arasındaki MiHR azalma oranı istatistiksel olarak bir farklılık göstermemiştir.

Sonuç: Sodyum valproat tedavisinin atrial ektopik atımlara etkili olduğu görülmektedir, dolayısıyla ektopik aritmi ve nöbet görülen hastalarda antiaritmitik olarak VPA'nın kullanılabileceği düşünülmektedir.

Anahtar Kelimeler: Sodyum valproat, holter ile gözlem, atrial ektopi, nöbet.

INTRODUCTION

Sodium valproate (valproic acid; VPA) is an anti-epileptic medication that is effective against several seizure types in adults and children; generalized, focal, myoclonic, and absence ones[1]. In addition, it can alleviate neuropathic pain[2] prevent migraine attacks[3] and has a mood-stabilizing effect[4] This broad-spectrum of action is explained by its various mechanisms of actions at the cellular level and at multiple sites; increased γ-aminobutyric acid transmission, reduced release and/or effects of excitatory amino acids, blockade of voltage-gated sodium channels, and modulation of dopaminergic and serotoninergic transmission[5]

Furthermore, several investigators reported an antiarrhythmic action of VPA on the cardiac conduction system[6-8].

MATERIALS and METHODS

This prospective, short-term longitudinal, observational study involved 80 consecutive patients who were recently diagnosed with cryptogenic generalized tonic-clonic seizures. The study was conducted at the Sulaimaniya General Teaching Hospital, Iraq from December 1, 2009 to June 1, 2011. Patients underwent a thorough history taking and clinical examination by internists and neurologists.

Inclusion criteria and initial work-up

Patients were enrolled in the study if they were 18 year (or older); had no cardiopulmonary disease; did not smoke or ingest coffee or tea excessively; taking no medication(s) which could influence the cardiac conduction system; had normal blood tests; and demonstrated normal 12-lead resting ECG (apart from atrial ectopic beats) and transthoracic echocardiography . Patients who developed seizures during the study period were excluded.

All patients (n=80) underwent a battery of investigations; routine blood tests (including thyroid function testing), resting 12-lead electrocardiography, transthoracic echocardiography, non- contrast CT brain scanning, and electroencephalography. None of them, however, underwent video EEG monitoring or a 3 Tesla MRI brain imaging. A 24-hour Holter monitoring was done in all cases at the time of enrollment and after week of therapy, using a 3-channel TLC9803 EKG Holter monitoring system, Contec Medical. A single well-trained technician did the attachment of the device and the analysis was done by cardiologists using a TLC9803 software version 5.1. The minimum and maximum heart rates as well as the total number of atrial ectopics in both groups were collected and compared.

Patients were divided into two groups; forty patients were given sodium valproate (Dépakine®, 200 mg and 500 mg tablet strengths, Sanofi-Aventis) in daily doses ranging from 400 to 800 mg. The second group was given a placebo; those patients were educated about the risk of developing seizures during the one-week period of study and they agreed to be enrolled; therefore, the randomization was not blinded. All patients/guardians/caregivers signed an informed consent. The hospital's human ethics committee approved the conduction of the study.

Statistical analysis

The collected data were organized, tabulated, and statistically analyzed by an independent statistician using Statistical Package for Social Sciences (SPSS) version 17. A comparison of the collected variables was performed by independent t-test, paired t-test, and correlation test. Significance

levels were set at p-value of less than 0.05 in all cases.

RESULTS

The various patients' characteristics are shown in table one while tables 2-6 display the statistical results and comparison in both groups. Figures 1 to 3 illustrate the MiHR, MaHR, and TNAE in both groups.

Forty seven (58.8%) patients were males (22 in the VPA group and 25 in the placebo group) while the rest (41.2%) were females (18 in the VPA-treated group and 15 in the placebo-treated group). In the VPA-treated group, the patients' ages ranged from 18 to 41 years with a median of 27 years while the ages of the patients in the placebo-treated group ranged from 18 to 43 years with a median of 28 years.

Sodium valproate therapy significantly reduced the MiHR (p<0.13; 95% CI, 1.5 to 11.8), MxHR (p<0.001; 95% CI, 9.5 to 22.8) and the TNAE (p<0.018; 95% CI, 55.7 to 559.4). In the placebo group, the reduction in the MiHR was statistically significant (p<0.02; 95% CI, 0.87 to 9.42) while the reduction in the MxHR (p<0.89; 95% CI, -8.28 to 723) and the TNAE (p<0.36; 95% CI, -46.1 to 125.3) were not. When both groups were evaluated for the reduction in the MiHR before (p< 0.68; 95% CI, -4.4 to 6.7) and after week of therapy (p<0.86; 95% CI, -4.2 to 3.5), there was no statistically significant difference between them. The daily doses of VPA ranged from 400-800 mg; the reduction in the target parameters in patients who received VPA did not seem to be dose-dependent (p<0.19).

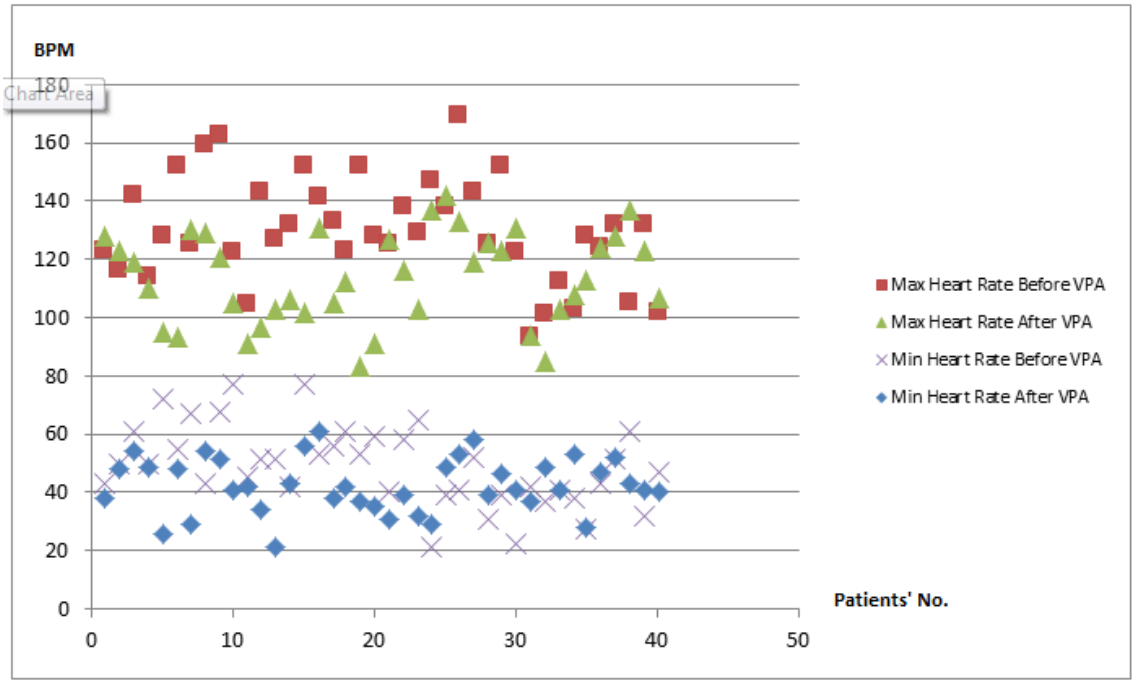

Figure 1. Minimum and maximum heart rates in patients before and after VPA administration (min, minimum; max, maximum; BPM, beats per minute).

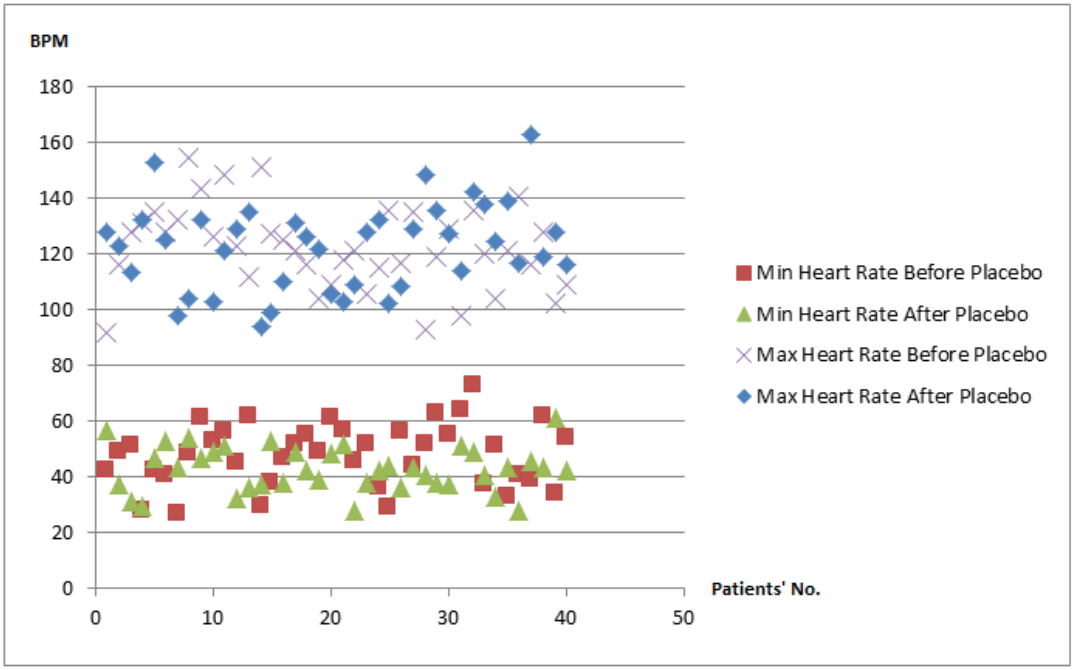

Figure 2. Minimum and maximum heart rates in patient before and after placebo administration (min, minimum; max, maximum; BPM, beats per minute).

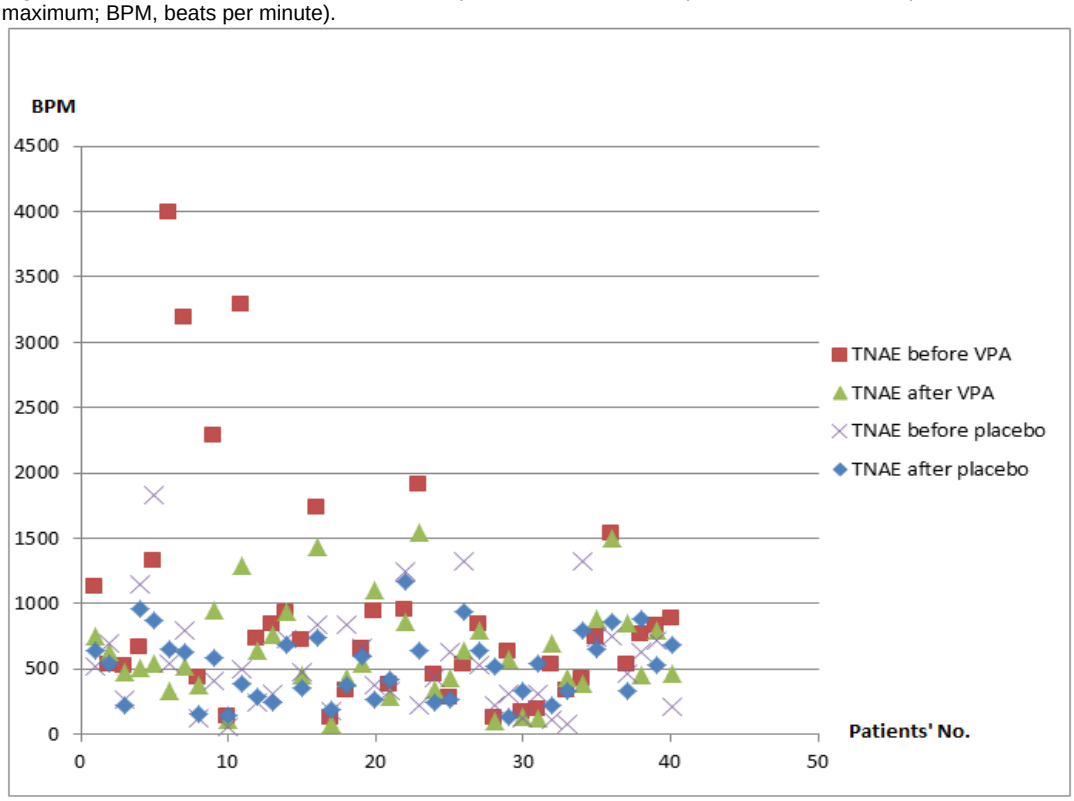

Figure 3. The total number of atrial ectopics in both groups, before and after VPA and placebo administration (TNAE, total number of atrial ectopics; BPM, beats per minute).

Table 1. Demographic characters of the cases enrolled in in the study (n=80).

Character	Group 1*		Group 2**		Total	
	No.	%	No.	%	No.	%
Gender						
Male	22	55	25	62.5	47	58.8
Female	18	45	15	37.5	33	41.2
Age (years)						
Minimum	18		18			
Maximum	41		43			
Median	27		28			
Occupation§						
Employed	5	12.5	8	20	13	16.2
Unemployed	8	20	6	15	14	17.5
Student	10	25	10	25	20	25
Worker	9	22.5	8	20	17	21.3
Housewife	8	20	8	20	16	20
Marital status						
Single	14	35	18	45	32	40
Married	26	65	22	55	48	60
Smoking						
Yes	12	30	11	27.5	23	28.7
No	28	70	29	72.5	57	71.2
Alcohol Drinking						
Yes	4	10	7	17.5	11	13.7
No	36	90	33	82.5	69	86.3
Coffee						
Yes	4	10	6	15	10	12.5
No	36	90	34	85	70	87.5

*This group (n=40) was treated with sodium valproate.

**This is the placebo-treated group; n=40.

§Employed= employee in the government sector; unemployed= works in the private sector (companies, small business); student= undergraduate or postgraduate student; worker=manual laborer; housewife= females who don't fit the aforementioned groups.

Table 2. Association of different variables for the two groups.

Variables	t-test	P value	95% confidence interval	
			Lowest	Highest
Holter 1* minimal heart rate	0.41	0.68§	- 4.4	6.7
Holter 1 maximum rate	2.1	0.04	0.5	15.2
Holter 1 number of ectopic	2.5	0.02	75.5	685.1
Holter 2** minimum heart rate	- 0.18	0.86§	- 4.2	3.5
Holter 2 maximum heart rate	- 2.5	0.01	- 15.8	- 1.8
Holter 2 number of ectopic	1.6	0.12§	- 30.6	255.2

* Holter1= Holter monitoring before the start of therapy in both groups. The association and statistical comparison were analyzed for each variable in both groups (head-t-head), i.e. minimum and maximum heart rates and the total number of ectopics.

** Holter2= Holter monitoring after the start of therapy in both groups. The association and statistical comparison were analyzed for each variable in both groups, i.e. minimum and maximum heart rates and the total number of ectopics.

§Not significant

Table 3: Association of different variables (before & after) for the sodium valproate treated group (n=40).

Variables	t-test	P value	95% confidence interval	
			Lowest	Highest
Holter 1* & 2** minimum heart rate	2.6	0.013	1.5	11.8
Holter 1 & 2 maximum heart rate	4.9	< 0.001	9.5	22.8
Holter 1 & 2 number of ectopic	2.5	0.018	55.7	559.4

*Holter 1=Holter monitoring before starting sodium valproate.

**Holter 2= Holter monitoring after starting sodium valproate.

Table 4: The correlation of different variables (before & after treatment) for the sodium valproate treated group (n=40).

Correlation	R	P value
Holter 1§ & 2¶ slowest heart rate	0.07*	0.67
Holter 1 & 2 minimum heart rate	0.24*	0.12
Holter 1 & 2 number of ectopic	0.46*	< 0.003

§Holter 1=Holter monitoring before starting sodium valproate.

¶Holter 2= Holter monitoring after starting sodium valproate.

*Not significant

Table 5: Association of different variables (before & after) for the placebo-treated group (n=40).

Variables	t-test	P value	95% confidence interval	
			Lowest	Highest
Holter 1§ & 2¶ minimum heart rate	2.44	0.02	0.87	9.42
Holter 1 & 2 maximum heart rate	- 0.14	0.89*	- 8.28	7.23
Holter 1 & 2 number of ectopic	0.94	0.36*	- 46.1	125.3

§Holter 1=Holter monitoring before starting sodium valproate.

¶Holter 2= Holter monitoring after starting sodium valproate.

* Not significant

Table 6: The correlation of different variables (before & after) for the placebo-treated group (n=40).

Correlation	R	P value
Holter 1§ & 2¶ minimum heart rate	0.06	0.72*
Holter 1 & 2 maximum heart rate	- 0.25	0.11*
Holter 1 & 2 number of ectopic	0.74	< 0.001

*Not significant

§Holter 1=Holter monitoring before starting sodium valproate.

¶Holter 2= Holter monitoring after starting sodium valproate.

DISCUSSION

Valproic acid is a 2-propylpentanoic acid, a branched chain carboxylic acid which has been shown to exert the following effects on various ion channels[9] It prolongs the recovery period of inactivated sodium channels; enhances potassium conductance and therefore results in hyperpolarization and inhibition of cells; and it reduces the currents of T-type (low threshold) calcium channels and this inhibits repetitive cellular firing. Accordingly, Pousti and colleagues[10] suggested that VPA exerts a direct cardiac action through these cellular mechanisms, which explains its antiarrhythmic effect.

In 1988, Meerson and coworkers[6] observed a direct action of VPA on the cardiac conduction system but the utility of this observation was not clear. Four years later, again, Meerson[7] studied the effect of VPA on cardiac ventricular premature complexes and found a strong evidence for the efficacy of VPA in patients with ventricular ectopics. Bing et al[8] analyzed the effect of VPA on the action potential of isolated cardiac papillary muscles of animals. They concluded that the effective refractory period was prolonged significantly but VPA showed no effects on action potential amplitude, overshoot, resting potential, or phase zero upstroke's velocity. Furthermore, Pousti[10] suggested that the membrane stabilizing effect of VPA is responsible for preventing atrial arrhythmia. In addition, Shabunina[11] studied the effect of VPA on rats with experimental myocardial infarction. He found that VPA prevents the drop of cardiac fibrillation electric threshold and restricts the development of extra-systole occurring in stimulation of the vagus nerve. Furthermore, Bowes et al[12] demonstrated an anti-atherosclerosis action of VPA in hyperglycemic apoE-deficient mice. It seems that VPA exerts cardiac electrophysiological and vascular effects according to the aforementioned studies in animals. However, Fedorov[13] concluded that experiments and drugs which had shown promising results on animals might not reproduce the same results on humans.

Atrial ectopic beats (or premature complexes) are common in young individuals without a structural heart disease or a pulmonary pathology; these beats can be completely asymptomatic and discovered only by resting 12-lead ECG or Holter monitoring[14-16] On the other hand, VPA has been shown to result in the following cardiovascular effects at therapeutic levels[17,18] hypertension, hypotension, postural hypotension, tachycardia and palpitation, vasodilatation, and dysrhythmia.

In our study, VPA significantly reduced the minimum and maximum heart rates and the total number of atrial ectopics. However, the placebo group also demonstrated a reduction in the parameter of minimal heart rate after one week but not in the maximum heart rate or the total number of atrial ectopics. The latter observation might be explained by the placebo effect as well as patients' intention to avoid excessive activity and coffee ingestion after being enrolled in the study, as patients and their treatment were not randomized blindly. However, a head-to-head comparison between the minimal heart rate after one week of treatment in both groups uncovered no statistically significant difference.

Sodium valproate was prescribed in doses ranging from 400 to 800 mg per day. We compared the reduction in the target parameters with respect to these total daily doses; we did not find a dose-dependent effect ($p<0.19$). We cannot confirm or refute that this dose-dependency does not exist, due to the fact that the number of the enrolled cases was small and that the difference in the ranges of the daily VPA doses was relatively narrow. Therefore, further analytic studies are required with respect to this "statistical finding."

Meerson et al[7] studied the antiarrhythmic action of VPA on ventricular, not atrial, ectopic beats in 22 patients and suggested that that VPA has a strong efficacy against these premature contractions which occur in the presence of neurocirculatory dystonia (inadequate

cardiovascular hyper-reactivity, and thus responses, to emotional stress[19].

Although we evaluated the effect of VPA therapy on atrial ectopics, but our finding is consistent with that of Meerson et al.[6,7].

CONCLUSION

Sodium valproate therapy appears to influence the cardiac conduction system and may be used as an antiarrhythmic medication in patients who co-experience seizures and troublesome atrial ectopics.

Limitations of the study

1. The number of the patients enrolled in this study was small. In spite of a relatively large number of epileptic cases diagnosed every month in Sulaimaniya city, Iraq, we selected only those who were experiencing troublesome cardiac ectopic beats. For the same reason, our patients were not randomized blindly to receive VPA or placebo. In addition, it is possible that the findings might have been different if the number of patients had been larger.
2. Some patients were smokers while others drank alcohol and/or coffee before the enrollment in the study. It is well-known that cardiac ectopic beats are augmented by these substances. Few patients admitted to reducing/abstaining the intake of these substances after their participation in the study. The impact of this event has not been evaluated in our study.
3. We did not co-analyze the effect of VPA on ventricular ectopic beats, which are also common in otherwise healthy population. Likewise, targeting heart rate variability was not an aim. These additional analyses, if they were done, might have changed the outcome of our study considerably.
4. Finally, most of the pertinent medical literature addressing our objective was in Russian language; their abstracts, only, were available in English and this made it difficult to appreciate their scientific content.

In summary

Our observation is consistent with that of Meerson et al,[6,7] but It should be emphasized that our finding does not support, though does not exclude, the usefulness of VPA therapy in alleviating cardiac atrial ectopic beats; however, whether this observation is clinically significant and that VPA can be used in the co-treatment of cardiac premature complexes or not, it has to be confirmed or refuted by further research.

Acknowledgements

We would like to thank our patients and their families; without their kind cooperation, this study would have not been accomplished. A special gratitude goes to Professor Jafri Malin Abdullah FACS FRCS(Edin), head of department of neurology, University Sains Malaysia; he had kindly provided us with very valuable comments and notes after reading the manuscript.

REFERENCES

1. Scollo-Lavizzari G, Proeckl D.Sodium valproate-still a current antiepileptic agent?. Praxis 1994;83:1098-105.
2. Agrawal RP, Goswami J, Jain S, et al. Management of diabetic neuropathy by sodium valproate and glyceryl trinitrate spray: a prospective double-blind randomized placebo-controlled study. Diabetes Res Clin Pract. 2009;83:371-8.
3. Spasic M, Zivkovic M, Lukic H. Prophylactic treatment of migraine with valproate. Med Biol 2003;10: 106-10.
4. El-Mallakh RS, Huff MO. Mood stabilizers and ion regulation. Harv Rev Psychiatry 2001; 9: 23-32.
5. Perucca E. Pharmacological and therapeutic properties of valproate: a summary after 35 years of clinical experience. CNS Drugs. 2002; 16:695-714.
6. Meerson FZ, Shabunina EV, Malyshev IIu. Direct cardiotropic anti-arrhythmic effect of sodium valproate. Kardiologiia. 1988; 28:100-2.
7. Meerson FZ, Gimrikh EO, Gutsol LIa, et al. The anti-arrhythmic efficacy of sodium valproate. Kardiologiia. 1992; 32:19-21.

8. Ding BC, Gao ZY, Wu M, et al. Comparison of effects of magnesium valproate and sodium valproate on the action potential of isolated papillary muscle from guinea pigs and dogs. J Tongji Med Univ. 1990; 10:248-52.

9. McNamara JO. Drugs effective in the therapy of the epilepsies. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG (Eds.) Goodman & Gilman's The pharmacological basis of therapeutics, 9th edition. New York: McGraw-Hill. 1996; 476.

10. Pousti A, Zare Jahromi A, Malihi G, et al. Effect of sodium valproate on ouabain-induced arrhythmia in isolated Guinea pig atria. Ira J Pharm Therap. 2007; 6:41-3.

11. Shabunina EV. [The effect of sodium valproate on the electrical stability of the heart in experimental myocardial infarct]. Patol Fiziol Eksp Ter. 1990; 23-5.

12. Bowes AJ, Khan MI, Shi Y, et al. Valproate attenuates accelerated atherosclerosis in hyperglycemic apoE-deficient mice: evidence in support of a role for endoplasmic reticulum stress and glycogen synthase kinase-3 in lesion development and hepatic steatosis. Am J Pathol. 2009; 174:330-42.

13. Fedorov VV, Glukhov AV, Ambrosi CM, et al. Effects of K(ATP) channel openers diazoxide and pinacidil in coronary-perfused atria and ventricles from failing and non-failing human hearts. J Mol Cell Cardiol. 2011; 51: 215-25.

14. Brodsky M, Wu D, Denes P, et al. Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. Am J Cardiol. 1977; 39:390-5.

15. Folarin VA, Fitzsimmons PJ, Kruyer WB. Holter monitor findings in asymptomatic male military aviators without structural heart disease. Aviat Space Environ Med. 2001; 72:836-8.

16. Dionne MV, Kruyer WB, Snyder QC Jr. Results of Holter monitoring U.S. Air Force aircrew with ectopy on 12-lead electrocardiograms. Aviat Space Environ Med. 2000;71:1190-6.

17. Lopinto-Khoury C, Mintzer S. Antiepileptic drugs and markers of vascular risk. Curr Treat Options Neurol 2010; 12:300-8.

18. Andersen GO, Ritland S. Life threatening intoxication with sodium valproate. J Toxicol Clin Toxicol. 1995; 33:279-84.

19. Sidorenko GI. Neurocirculatory dystonia (does this disease exist?). Kardiologiia. 2003; 43:93-8.

Yazışma Adresi / Address for Correspondence:
Dr. Osama Shukir Muhammed Amin
Sulaimaniya Post-Office, PO BOX 196,
Sulaimaniya City, Iraq
E-mail: dr.osama.amin@gmail.com.

geliş tarihi/received :20.02.2013
kabul tarihi/accepted:25.03.2013