ORIGINAL ARTICLE

HOMEOSTATIC CHANGES DURING ANTICONVULSANT MEDICATION IN CHILDREN

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Abstract

Approximately 3% of the paediatric population presents one seizure episode till the age of 15, half of which are associated with fever [8]. Around 1% of children exhibit epilepsy-recurring seizures. Although having known side effects, carbamazepine and valproic acid still hold supremacy in the hierarchy of anticonvulsant therapy. The aim of this study was to establish the prevalence of abnormal haematological and biochemical values in children receiving carbamazepine or valproic acid therapy who attended Clinical Emergency Hospital for Children, Galati, Romania, assessing the vulnerability of the paediatric population to the side effects caused by this type of medication. Moreover, simultaneous measurement of serum concentrations of carbamazepine and valproic acid represents a practical way of assessing the quality of treatment, facilitating dose adjustment in order to obtain an optimum cost/therapeutic benefit ratio.

Rezumat

Aproximativ 3% din popula/ia pediatrică înregistrează un episod convulsiv până la vârsta de 15 ani, din care jumatate se asociază cu febra [8]. În jur de 1% din copii manifestă convulsii epileptice recurente. Deşi sunt cunoscute ca având reacţii adverse, carbamazepina şi acidul valproic deţin încă supremaţia în ierarhia substanţelor active ce stau la baza terapiei anticonvulsivante. Scopul acestui studiu a constat în stabilirea prevalenței modificărilor parametrilor hematologici și biochimici la copiii aflați sub terapie cu carbamazepină și acid valproic, internați la Spitalul Clinic de Urgență pentru Copii din Galați România, evaluând gradul de vulnerabilitate a populației pediatrice la reacțiile adverse produse de acest tip de medicaţie. Totodată, măsurarea concomitentă a concentraţiei serice a carbamazepinei şi acidului valproic oferă un mijloc concret de apreciere a calităţii tratamentului, facilitând ajusarea dozelor în vederea obţinerii unui raport cost/beneficiu terapeutic optim pentru pacient.

Keywords: valproic acid, carbamazepine, side effects, children

Introduction

Carbamazepine (CBZ) and valproic acid (VPA) still keep an important place in anticonvulsant therapy even if new drugs have been recently approved. The physicians should be aware of the peculiarities of anticonvulsant (ACV) drug administration in paediatric population as there are certain physiological features that influence the pharmacokinetics of drugs (reduced gastric acidity, low quantity of fatty tissue, reduced binding of plasma proteins, increased permeability of biological barriers, underdeveloped enzyme equipment and reduced renal excretion).

CBZ is a tricyclic compound that blocks the sodium channels at therapeutic concentrations and potentiates postsynaptic action of GABA. Used to treat partial or generalized tonic-clonic seizures, CBZ exhibits almost complete absorption. VPA is a carboxylic acid that, like CBZ, blocks sustained high-frequency repetitive firing of neurons in culture at therapeutically relevant concentrations. Valproate increases levels of GABA in the brain by facilitating its synthesis and blocking its degradation [5]. Used especially in absence of seizures, valproate's bioavailability is greater than 80% and its absorption is delayed by food. Therefore, in case of ACV treatment, physicians

should pay attention to a wide range of factors: drug's metabolism inhibition, level of plasma proteins, the increase of the distribution volume and free drug concentration for patients with hepatic or renal impairment [4], dose-related side effects, drug interactions [10], individual treatment response variation due to genetic polymorphisms [17]. The serum concentrations of CBZ were proven to reflect more accurately the clinic response to therapy as compared to the dosage [12].

To sum up, the physiological particularities of children call for ACV treatment monitoring and proactive adjustment of the clinical approach, while always keeping the paediatric patient's overall welfare in focus.

Materials and Methods

A prospective observational study was conducted on 54 children aged below 18 years, admitted to the Clinical Emergency Hospital for Children, Galati (Romania). Subjects were treated with VPA 35 mg/kgbw/day or CBZ 20 mg/kgbw/day. The investigation ended after 8 months (1.01.2012-1.09.2012) of treatment or whenever a patient's treatment had to be prematurely ceased, regardless of motivation.

The study was approved by the Ethical Committee of the 'Dunarea de Jos" University and the Clinical Emergency Hospital for Children, Galati, and was carried in accordance with standard operation procedures which ensure Good Clinical Practice. Written informed parental consent was obtained before admission to the study.

In order to be eligible for the study, each subject had to meet the following inclusion criteria: age below 18, administration of VPA (Depakine®) 35 mg/kgbw/day or CBZ (Carbamazepine®, Timonil®, Taver®) 20 mg/kgbw/day, and stable clinical status. The exclusion criteria consisted of evidence of non-adherent behaviour, severe adverse effects associated with the discontinuation of the therapy and the administration of any systemic medication that interacts with VPA or CBZ, grapefruit juice ingestion three days before the determination of drug serum concentrations.

Two blood samples were taken from each subject in order to perform haematological and biochemical investigations. Measurements for haemoglobin, haematocrit and thrombocyte number were made using a *Celltac alfa MEK 6400K* haematology analyser *(Nihon Koden, Japan)*.

Serum ammonium ions, liver enzymes, urea, creatinine, carbon dioxide (ECO2), sodium ions, potassium and chloride concentrations were measured by the *MicroSlides* method using *J&J Vitros 950* chemistry analyser *(Ortho-Clinical Diagnostics, USA)*. Serum concentrations of CBZ and VPA were quantified simultaneously using *RX Imola* analyser (immunoturbidimetric method). Anion gap (AGap) and osmolarity were calculated using standard formulas.

Statistical analysis. The results were expressed as mean ± standard deviation of three replicates. The statistical analysis was performed using analysis of variance (ANOVA) one way. Mann-Whitney test was used for multiple comparisons (software Stats Direct version 2.6). A value of $p < 0.05$ was considered significant.

Results and Discussion

The study population comprised 54 subjects, 36 of which received VPA treatment, 15 CBZ treatment, and 3 both ACVs treatment. The lot included 66.66% males and 33.33% females with a mean age of 10.07 ± 5.18 years (Table I). Most of patients come from urban area (72.22%) whereas 9 patients (27.77%) come from the rural area.

Table I

Registered patients' age and ACV serum concentration

Parameter	*Mean*	*Std.Dev*	*Range*	*Outliers**	*Reference*
Group age (years)					
VPA	*9.32*	*5.35*	*1-18*		
CBZ	*12,5*	*3.85*	*5-18*		
VPA+CBZ	*8*	*6.56*	*2-15*		
Serum concentration (mg/dL)					
VPA	*53.23*	*33.11*	*22.76-102.35*	*15L, 1H*	*50-100*
CBZ	*6.14*	*6.24*	*0.15-19.53*	*5L, 2H*	*4-12*
VPA+CBZ (VPA)	*33.23*	*36.97*	*0.48-73.32*	*2L*	
VPA+CBZ (CBZ)	*7.84*	*1.98*	*5.68-9.57*		

**L = low, H = high*

The measurement of the serum concentration of ACV showed that VPA reached 53.23 ± 33.11 µg/mL in patients who received VPA and 33.23 ± 36.97 µg/mL in patients who received treatments both with VPA and CBZ. Comparing to reference range for VPA (50-100 µg/mL), our data analysis reveals 15 cases of underdosing medication and one case of overdosing therapy. The serum concentration of CBZ was 6.14 ± 6.24 µg/mL in patients who received only CBZ and 7.84 ± 1.98

µg/mL in those with VPA-CBZ combined therapy. Serum concentration of CBZ was below the reference range (4-12 µg/mL) in 5 of the investigated subjects and above the reference range in 2 subjects. Either CBZ or VPA proved high standard deviation of the serum concentrations, related to the pharmacokinetic variations. The individual toxicity, therapeutic efficacy and quality of life are influenced by the drugs levels [9, 13].

Our results agree with literature data that indicated that VPA inhibits the metabolism of CBZ, increasing steady-state carbamazepine blood levels [4]. On the other hand, CBZ induced cytochrome P450 enzymes which can cause and an increased rate of metabolism of VPA.

Haematological investigation revealed the presence of anaemia in 10 (18.5%) patients receiving VPA treatment, 3 (5.5%) patients receiving CBZ treatment and 1 (1.8%) patient receiving both VPA and CBZ treatment (Table II). Anaemia accompanying ACV treatment as well as clotting abnormalities under VPA treatment have also been indicated by Jerrel et al. and Ünal et al. [6, 15]. However, considering the estimated 27% prevalence of anaemia in Romanian children under 5 years old, the association of anaemia and anticonvulsant therapy does not appear significant. Moreover, the comparative baseline haematological values were not systematically available [16].

Platelet count revealed two cases of thrombocytopenia (under VPA treatment) and 1 case of thrombocytosis under CBZ treatment. Nasreddine's data indicate that 17.7% of patients receiving VPA treatment experienced at least one episode of thrombocytopenia, women being more exposed than man [8].

Table II

Results of the haematological investigations

Parameter	*Mean*	*Std. Dev.*	*Range*	*Outliers*[*]	*Reference*
Hb (g/dL)					
VPA	*12.24*	*1.18*	*9.9-14.6*	*10 L*	*11.5-15.5*
CBZ	*12.61*	*1.39*	*10.4-15*	*3 L*	
VPA+CBZ	*12.7*	*0.72*	*11.9-13.3*	*1 L*	
Ht (%)					
VPA	*36.76*	*2.99*	*30.5-42.8*	*10 L*	*36-39*
CBZ	*37.89*	*2.81*	*34.2-43.2*	*3 L*	
VPA+CBZ	*36,47*	*1.98*	*34.7-38.6*	*1 L*	
Platelets (no./µL)					
VPA	*265.03*	*133.91*	*50.08-289*	*2 L*	*150-300·10*^{3}
CBZ	*287.75*	*54.84*	*193-363*	*1 H*	
VPA+CBZ	*296.33*	*115.63*	*184-286*		

[*] *L = low, H = high*

Our results indicate that protein levels, urea and creatinine serum levels were within the normal results range (data not shown) and that 4 patients on VPA treatment exhibited increased ALT and AST levels. A number of 5 patients who received VPA experienced gastrointestinal complaints, 2 patients receiving CBZ experienced ataxia, 6 patients on CBZ experienced restlessness and 1 patient receiving both CBZ and VPA experienced erythematous skin rash. Our data are in agreement with literature that indicates that most common adverse effects for CBZ are diplopia and ataxia, hyponatremia and water intoxication, idiosyncratic blood dyscrasia and erythematous skin rash. Another study also indicated that carbamazepine may associate excess behavioural side effects such as sleep disturbance, gastrointestinal problems severe headache and worsening of seizures in childhood epilepsy [1]. The presence of drowsiness, loss of coordination, and vertigo is although well known as reaching most than a half of patients receiving CBZ medication, either children or adults, seeming to have a close connection with the drug dose [11].

The most frequent adverse effects of valproate are gastrointestinal complaints, hepatotoxicity, and thrombocytopenia. A fine tremor, weight gain, hair loss and sedation can be also observed in the administration of high doses.

Serum chemistry results are presented in Table III. The chloride level exceeded the normal range in 6 children (11.11%), corresponding to 16.6% VPA patients and 33.3% both CBZ and VPA+CBZ patients. Sodium ions concentration increased in 22 children (40.7%) – 39% VPA subject and 53% CBZ subjects, respectively. Excepting 3 patients, serum potassium concentration was within normal ranges. Acidosis was identified in 22 cases (40.7%), with a similar frequency between VPA patients (44.4%) and CBZ patients (40%). Valproic acid alters fatty-acid metabolism, impairs beta-oxidation leading to metabolic imbalances like hyperammonemia. In our study, elevated ammonium concentration was present in 8 of the investigated subjects (14.8%). Osmolarity exceeded

high range limit (280 mOsm/kg) in only 7 subjects (12.9%): 5/VPA and 2/CBZ. It can be assumed that the increase of the ammonium concentration could be considered as a warning signal for advanced subsequent disturbances of renal and hepatic function. In this context, the use of arginine and aspartic acid to counteract hyperammonemia, could be useful [2, 14].

Increasing daily water intake could sustain body homeostasis regulation under anticonvulsant treatment.

In a previous study [3], anaemia and hydroelectrolyte imbalances were found in a mentally-disabled paediatric population, of which some patients were receiving ACV treatment, but insufficient data prevented correlations being established. Recent molecular studies show that drug disposition and/or response is strongly related to genetic polymorphisms of cytochrome P450 enzymes. Carbamazepine can trigger an immune reaction also, proven by the presence of the human leukocyte antigen (HLA)-B*1502 allele [7]. Under these conditions, pharmacogenomic testing could become a practical method for explaining the variety of clinical and paraclinical manifestations in patients receiving ACV drugs.

Table III

Results of the biochemical investigation

Parameter	*Mean*	*Std.Dev.*	*Range*	*Outliers**	*Reference*
ALT	37.73	20.115	10-97	4 H	
AST	36.81	14.92	7-89	4 H	
Osmolarity (mOsm/kg)					
VPA	274.00	10.37	245.3-294.35	5	>280
CBZ	274.41	6.91	256.55-283.67	2	
VPA+CBZ	267.36	2.76	264.18- 269.20		
Sodium (mmol/L)					
VPA	144.93	5.56	130-154	14 H	135-145
CBZ	145.58	4.54	135-152	8 H	
VPA+CBZ	140	1.73	139-142		
Potassium (mmol/L)					
VPA	4.46	0.43	3.5-5.4	2 H	3.5-5
CBZ	4.11	0.45	3.5-5		
VPA+CBZ	4.70	0.61	4.3-5.4	1 H	
Chloride (mmol/L)					
VPA	106.21	4.80	99-114	6 H	95-100
CBZ	106.42	5.76	98-114	5 H	
VPA+CBZ	105.33	7.02	98-112	1 H	
Alkaline reserve (mmol/L)					
VPA	22.75	3.19	17-29		
CBZ	22.08	3.34	18-28		
VPA+CBZ	23	2.65	21-26		
Anion gap (mmol/L)					
VPA	17.46	6.96	5-31	16	>15
CBZ	17.08	7.40	1-27	6	
VPA+CBZ	11.67	3.06	9-15		
NH_4^+ (µmol/L)					
VPA	49	14.47	32-76	6	**>33**
CBZ	46.86	16.93	23-73	1	
VPA+CBZ	40	40.67	40-42	1	

**L = low, H = high*

Conclusions

The study highlighted the input that can be provided by monitoring the anticonvulsant therapy administered to a paediatric population, enabling an assessment of clinical response which can be correlated with drug serum levels. Adjustments of anticonvulsants dosing to the specific therapeutic goals must take into account intra- and/or inter-individual variability. However, the study revealed a number of changes in haematological parameters, acid-base and hydric disturbances which, considering the childhood onset and the prolonged duration of treatment, could generate large-scale complications in adulthood. Increasing daily water intake could sustain body homeostasis regulation while under anticonvulsant treatment.

Hopefully, this study will spark further interest in monitoring ACV treatment in children both from the perspective of drug serum availability as well as

that of the homeostatic alterations induced by treatment.

References

1. Banu S.H., Jahan M., Koli U.K., Ferdousi S., Khan N.Z., Neville B., Side effects of phenobarbital and carbamazepine in childhood epilepsy: randomised controlled trial. *BMJ*, 2007; 334(7605): 1207. doi:10.1136/bmj.39022.436389.BE.
2. Crisan E., Ramachandran T.S., Hyperammonemia Treatment & Management. *Medscape Reference Drug, Diseases & Procedures*, updated 2012, online, URL: http://emedicine.medscape.com/article/1174503-treatment#showall.
3. Dobre M., Popa P., Nechita A., Georgescu L.P., Clinical and paraclinical aspects in mental retardation and autism spectrum disorders. *Revista Română de Medicină de Laborator*, 2009; 16(3):59-69.
4. Gidal B.E., Chapter 22 - Valproic Acid, In: Clinical Pharmacokinetics, 5th Edition, 2011, 327-336, American Society of Health-System Pharmacists Inc, ISBN 978-1-58528-254-8.
5. Goodman & Gillman's Manual of Pharmacology and Therapeutics, Ed. Brunton L, Parker K., Blumenthal D, Buxton I, 2008:319-329, ISBN 978-0-07144343-2.
6. Jerrell J.M., Tripathi A., Stallworth J.R., Pain management in children and adolescents with sickle cell disease. *American Journal of Hematology*, 2006; 86: 82-84.
7. Ma J.D., Lee K.C., Kuo G.M., Clinical application of pharmacogenomics. *J. Pharm. Pract.*, 2012; 25(4): 417-427.
8. Nasreddine W., Beydoun A., Valproate-induced thrombocytopenia: a prospective monotherapy study. *Epilepsia*, 2008; 49(3): 438-445.
9. Nicolae A.C., Mitrea N., Dragoi C.M., Constantinescu M.Z., Ciofrangeanu C., Barboi G., Arsene A.L., Murine studies regarding the variation of oxidative status in serum, hepatic and brain samples, after administration of some CNS active drugs. *Farmacia*, 2013; 61(4): 658-669.
10. Paul S.P., Blaikley S., Chinthapalli R., Clinical update: febrile convulsion in childhood. *Community Pract.*, 2012; 85(7): 36-38.
11. Pellock J.M., Carbamazepine side effects in children and adults. *Epilepsia*, 1987; 28(3): S64-70.
12. Perucca E., An Introduction to Antiepileptic Drugs. *Epilepsia*, 2005, 46(4): 31-37.
13. Seblany H.T., Dinu I.S., Safer M., Plesca D.A., Factors that have a negative impact on quality of life in children with ADHD. *Farmacia*, 2014; 62(2): 350-357.
14. Summar M., Current strategies for the management of neonatal urea cycle disorders. *J. Pediatr.*, 2001ş 138(1): S30-39.
15. Ünal Ö., Deda G., Teber S., Ertem M., Akar N., Thrombophilic Risk Factors in Epileptic Children Treated with Valproic Acid. *Pediatr. Neurol.*, 2009; 40: 102-106.
16. Stevens G.A., Finucane M.M., De-Regil L.M., Paciorek C.J., Flaxman S.R., Branca F., Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. *Lancet*, 2013; 1(1): e16–25. doi: 10.1016/S2214-109X(13)70001-9.
17. Zhou S.F., Liu J.P., Chowbay B., Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metab. Rev.*, 2009; 41(2): 89-295. doi: 10.1080/03602530902843483.