ORIGINAL PAPER

doi: 10.5455/medarh.2017.71.239-242

MED ARCH. 2017 AUG; 71(4): 239-242

RECEIVED: JUN 15, 2017 | ACCEPTED: AUG 04, 2017

Effects of Carbamazepine and Valproate on Serum Aspartate Aminotransferase, Alanine Aminotransferase and Gamma - Glutamyltransferase in Children

Feriha Hadzagic-Catibusic, Edo Hasanbegovic , Melika Melunovic, Smail Zubcevic, Sajra Uzicanin

Pediatric Clinic, University Clinical Center of Sarajevo, Bosnia and Herzegovina

Corresponding author: Feriha Hadzagic Catibusic. Patriotske lige 81, 71 000 Sarajevo, Bosna and Hercegovina. Tel. 00 387 33 566 446. Fax. 00387 33 566 525, E-mail:feriha1106@gmail.com

ABSTRACT

Introduction: Epilepsy is one of the most common neurological diseases in childhood and adolescence. Carbamazepine (CBZ) and valproate (VPA) have been widely used as the first generation of antiepileptic drugs (AED). **Aim:** The aim of the study has been to evaluate and compare the effect of CBZ and VPA monotherapy on aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) serum levels in children. **Material and methods:** The study has included 100 patients (boys 57/girls 43, age range 1 to 18 years),who have been treated with CBZ or VPA, as initial monotherapy, for at least 12 months. Patients with liver lesions or patients who have been treated with other drugs have been excluded from the study. The initial serum enzyme levels (AST, ALT and GGT) and after 12 months of treatment have been compared. **Results:** 53/100 (53%) patients have been treated with CBZ and 47/100 (47%) patients have been treated with VPA.The initial level of enzymes were within the referece range. After one year-long treatment AST was elevated at 4/53 (7.5%) CBZ patients and 9/47 (19.15%) VPA patients (x2 test =3.965, $p<0.05$). ALT was elevated at 5/53 (9.4%) CBZ patients and 9/47 (19.15%) VPA patients (x2 test =6.953, $p<0.05$). GGT was elevated at 18/53 (34%) CBZ patients and 7/47 (14.9%) VPA patients (x2 test =4.831, $p<0.05$). **Conclusion:** The levels of enzymes AST and ALT have been elevated statistically significant in VPA group and GGT in CBZ group.

Keywords: valproate, carbamazepine, aspartate aminotransferase, alanine aminotransferase , gamma-glutamyl transferase, child.

1. INTRODUCTION

Epilepsy is the most common neurological disease in childhood and adolescence. It is defined by any of the folowing conditions: At least two unprovoked (or reflex) seizures occuring >24 h apart, one unprovoked (or reflex) seizure and a probability of further seizure similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occuring over the next ten years and diagnosis of an epilepsy syndrome (1)

The first generation AEDs, valproate (VPA) and carbamazepine (CBZ) have been widely used in childhood population .

CBZ stabilizes voltage-gated sodium channels (VGSCs), by inhibition of of sodium channel activity (2-4).

Valproic acid (2-propylpentanoic acid) affects the GABAergic system, inhibits α-ketoglutarate dehydrogenase (αKGD), GABA transaminase (GABA-T) and succinate semialdehyde dehydrogenase (SSD). It also enhances glutamate decarboxylase (GAD) to elevate GABA levels in plasma and in several brain regions.

CBZ and VPA have been widely used AED for focal and generalized seizures (5).

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are intracellular enzymes which can be found in cytosol and mitochondria. They are normally found in the plasma at low levels.

ALT is intracellular enzyme found predominantly in the liver, while AST is found in the liver, heart, skeletal muscle, kidneys, brain and erythrocytes. In asymptomatic patients, the most frequent causes of elevated transaminases were drug induced liver injuries. The elevation

can be secondary to enzyme induction, without hepatic pathology (6, 7).

Gamma glutamyl transferase (GGT) is an enzyme located on the external surface of celluar membranes of many tissues mainly in the liver, kidney, and pancreas. GGT is present in all cells with the exception of erythrocytes.

GGT is a cell-surface protein contributing to the extracellular catabolism of glutathione (GSH). GGT contributes in maintaining the physiological concentrations of cytoplasmatic glutathion and cellual defense against oxidative stress. Increased GGT activity is a marker of antioxidant inadequacy and increased oxidative stres (8).

Circulating GGT is supposed to originate mostly from the liver and is influenced by genetic and environmental factors.

Gamma-glutamyltransferase activity is inducible by drugs. GGT levels may be increased due to medications, such as carbamazepine, cimetidine, furosemide, heparin, isotretinoin, methotrexate, oral contraceptives, phenobarbital, phenytoin, and valproic acid (9).

Increases in GGT activity can be a response to oxidative stress, facilitating increased transport of glutathione (GSH) precursors into cells. In addition, GGT is leaked into the serum possibly as a result of normal cell turnover and cellular stresses.

Serum GGT traditionally has been used as a marker of alcohol-induced liver disease. Recently, GGT has been regarded as a clinical marker for free-radical formation and proinflammation. GGT-related pathomechanism is that GGT enhances the availability of cysteine to promote intracellular glutathione, the principle thiol antioxidant in humans, and resynthesis, thereby counteracting oxidant stress (10).

2. AIM

The aim of the study has been to evaluate and compare the effect of CBZ and VPA monotherapy on enzymes AST, ALT and GGT serum levels, after one year of treatment.

3. MATERIAL AND METHODS

This was a hospital-based, analytical cross-sectional study carried out by the inpatient and outpatient ward of Pediatric hospital, Clinical Center of Sarajevo University.

The study has included patients with epilepsy, both genders, age 1-18 years, treated with CBZ or VPA regularily, as initial antiepileptic monotherapy, for 12 months at least. All patients treated with valproate or carbamazepine had drug concentrations within the therapeutical level. Patients receiving more than one AED, patients on irregular antiepileptic medication and patients who were treated with other drugs were excluded from the study.

The patients with liver lesions and other chronic diseases were also excluded from the study. The level of AST, ALT and GGT enzymes have been checked before the initiation of therapy and only patients with reference values have been included. The level of enzymes has been checked up regularely, and compared after 12 months of treatment. The enzyme analyzes have been done with Dimension Xpant Simens machine.

The blood samples were drawn from peripheral veins after minimal fasting period of 6 hours for children till the age of 3 years and midnight fast for older children.

The referance values for enzymes were: AST 7-38 IU/L, ALT 8-41 IU/L, GGT 8-40 IU/L.

4. RESULTS

The distribution of the patients according to the age was: 1-4 years 7/100 (7%), 5-9 years 25/100 (25%), 10-14 years 42/100 (42%), 15-18 years 26/100 (26%).

The distribution of the patients according to the gender was: 57/100 (57%) boys and 43/100 (43%) girls; x2 test ==0,204; p=0,651; p>0,05

According to the AED used for treatment, the patients have been divided into two groups: patients treated with carbamzepine, CBZ group (53/100, 53%) and patients treated with valproate, VPA group (47/100, 47%); x2 test =0,048; p=0,826; p>0,05 (Table 1).

	N	%
Valproate	47	47,0
Carbamzepine	53	53,0
Total	100	100,0

Table 1. Distribution of patients according to the AED. x2 test=0,048; p=0,826

The serum levels of AST have been within reference values at 49/53 (92, 5%) patients in CBZ group and 38/47 (80.9%) patients in VPA group.

The serum levels of AST have been elevated at 4/53 (7.5%) CBZ patients and 9/47 (19.1%) patients in VPA group; x2 test =3.965; p=0,045; p<0,05 (Figure 1).

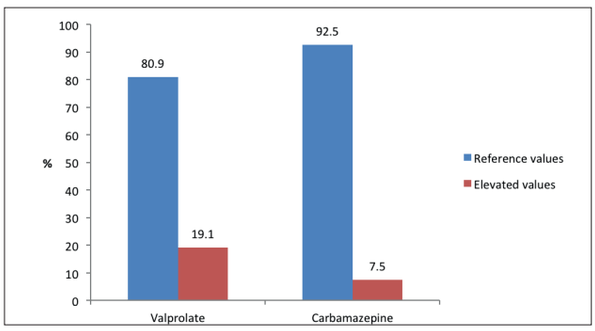

Figure 1 .The levels of AST after one year of treatment. x2 test =3.965; p=0,045

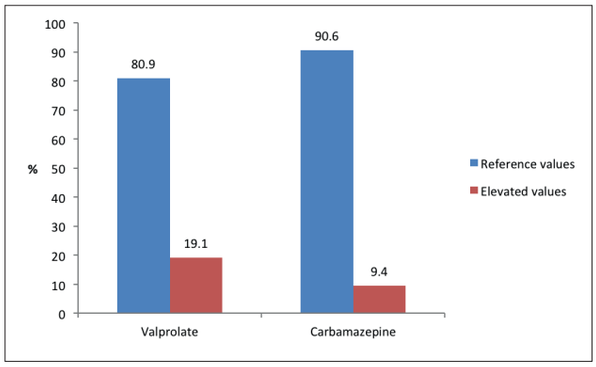

Figure 2.The levels of ALT after one year of treatment. x2 test =6.953; p=0,0162

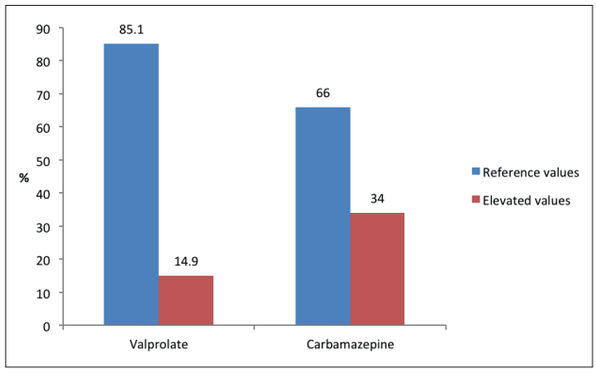

Figure 3. The levels of GGT after one year of treatment. x2 test =4.831; p=0,027

The serum levels of ALT have been within reference values at 48/53(90.6%) patients in CBZ group and 38/47 (80.9%) patients in VPA group.

The serum levels of ALT have been elevated at 5/53 (9.4%) CBZ patients and 9/47 (19.1%) VPA patients; x2 test =6.953; p=0,0162; p<0,05. (Figure 2).

The serum levels of GGT have been within reference values at 35/53(66%) patients in CBZ group and 40/47 (85.1%) patients in VPA group.

The serum levels of GGT have been elevated at 18/53 (34%) CBZ patients and 7/47 (14.9%) VPA patients; x2 test =4.831; p=0,027; p<0,05 (Figure 3).

5. DISCUSSION

The study has included 100 patients with epilepsy. The complete diagnostic work up have been done before the medical treatment with carbamazepine or valproate has started.

The distribution of patients according to the age was as follows: the age group 10-14 years was the largest (42%) and the age group 1-4 years (7%) was the smallest.

According to the gender distribution, there is no stastistically significant difference between boys and girls (x2 test ==0,204; p=0,651; p>0,05). The distribution of patients according to the AED used for treatment has no stastistically significant difference between CBZ and VPA group (x2 test =0,048; p=0,826; p>0,05) .

Carbamazepine (CBZ) is extensively bio-transformed in the liver via the action of enzymes of cytochrome P 450 system (CYP 450). CBZ 10.11-epoxide (CBZ-E), which possesses anti-convulsant properties is generated through the action of CYP3A4, CYP3A5 and CYP2C8 (11).

CYP P450 is a family of 40-50 isoenzymes responsible for the biotransformation of several drugs. These isoenzymes are membrane proteins, which are located in the smooth endoplasmatic reticulum of several tissues. CYP3A4 and CYP3A5 represent 65% of isoforms in the cytochrome P450 enzyme system and they interact with more than 60% of licensed drugs (12). CYP3A4 has the greatest abundance in the liver and intestine and is responsible for the metabolism of the largest number of clinically used drugs, as well as range of endognous substrates such as prostaglandines, steroid hormones and fatty acids (9).

Each isoenzyme is derived from the expression of an individual gene. CYP3A4 and CYP3A5 exhibit the most individual variations of gene expression, mostly due to single nucleotide polaymorphism. Individual variations in single nucleotide polymorphism within the regulatory genes of CYP3A4 and CYP3A5 might affect the level of enzyme production (12-14).

Cytochrome P450 (CYP450) isoenzymes are induced by AEDs, especially the classical AEDs, such as benzodiazepines (BZDs), carbamazepine (CBZ), phenytoin (PT), phenobarbital (PB) and valproic acid.

Carbamazepine is potent inducer of CYP 450 enzymes. Enzyme induction is mediated through the binding of one or more chemical activators to CYP isoenzyme intracellular receptors, ultimately producing increased transcription of CYP genes (9). In that way, CBZ induces its own metabolism (autoinduction) that starts within 24 h of the initiation of therapy. A transient and asymptomatic elevation of liver enzymes occurs in 25-61% of patients receiving CBZ.

Long- term use of CBZ may induce CYP 450 enzyme system to accelerate metabolism of vitamin D to inactive metabolites, with consequent reduction of active form of vitamin D (9, 11).

Carbamazepine is known to accelerate the metabolism of thyroid hormones too, by inducing of the hepatic P450 enzyme system which causes increased metabolism of thyroid hormones, thus accelerating clearance of thyroid hormone, with result of subclinical hypothyroidism (15).

Erythromycin, clarithromycin, and triacetyloleandomycin are potent CYP3A4 inhibitors and should be avoided in CBZ-treated patients. Azithromycin does not interact with CYP3A4 and, therefore, does not affect CBZ concentrations.

CBZ is potent inducer of AST, ALT and GGT, as well. The elevation of serum levels of AST,ALT and GGT, without any signs and symptoms of liver injury can be explained as a result of enzyme induction, without hepatic patology (7). Valproate (VPA) has very complicated biotransformation. Hepatic biotransformation is the main route of elimination and involves glucuronization, b-oxidation and CYP 450 mediated oxidation 30%–50% of VPA may be metabolized via glucuronization, 30% of VPA metabolism occurs via β-oxidation in the mitochondria and 10% of VPA is biotransformed through CYP450-mediated oxidation (11).

Moreover, VPA can inhibit histone deacetylase (HDAC), which is crucial factor in the pathogenesis of cancer and transcriptional regulation. VPA, as well as other HDAC inhibitors is able to alter expression of many genes involved in the modulation of cell growth, differentiation, and apoptosis (11, 16).

During the study period of 12 months, the serum levels of AST,ALT and GGT have been checked up regularily. The enzyme levels after 12 months of treatment have been analyzed. AST was elevated at 19.1% VPA treated patients and 7.5% CBZ treated patients, (x2 test =3.965; p=0,045; p<0,05), with statistically sinificant AST elevation in VPA group.

After 12 months of treatment, ALT was elevated at 19.1% VPA treated patients and 9.4% CBZ treated patients (x2 test =6.953; p=0,0162; p<0,05). There is statistically significant ALT elevation in the VPA group (Figure 2).Those results are similar to those published by Hussein R. et al (7).

The serum level of GGT was elevated at 7/47 (14.9%) VPA treated patients and 18/53 (34%) CBZ treated patients. (x2 test =4.831; p=0,027; p<0,05). There is statistically significant GGT elevation in the CBZ group.

Serum levels of GGT are determined by several factors: alcohol intake, body fat content, plasma lipid/lipoproteins, glucose levels, and various medications.

GGT also has an intracellular antioxidant effect because it is involved in gluthathione metabolism, resulting in the formation of cystein, a thiol compound that exerts antioxidant effects. GGT is cleared from the plasma by liver uptake.

GGT has a half-life of 10 days; however, in recovery from alcohol abuse, the half-life may be as long as 28 days.

It is well-known that administration of carbamazepine and valproate may cause the elevation of serum levels of AST, ALT and GGT in adults, but there are limited data about their influence in children.

Carbamazepine and valproate have different metabolisam. The CBZ has been biotransformated via CYP 450 system only, while valproate has been metabolized via glucuronization and β oxidation mostly and only 10% of valproate has been metabolized via CYP 450 system. On the cell level, carbamzepine has been metabolized through smooth endoplasmatic reticulum, while valproate has been metabolized through endoplasmatic reticulum and motochondria. It is quite possible that complexity of valproate metabolisam may cause ASTand ALT elevation more often, than metabolisam of carbamazepine.

The explanation for GGT elevation may be found in the fact that carbamazepine is potent enzyme inducer and thus may explain increase in synthesis of GGT. Carbamazepine influence on CYP 450 system has been studied a lot, with special interest on genetic polimorphism of CYP 3A4 and CYP 3A5 genes.

In our study the elevation of AST, ALT and GGT was mild and asymptomatic in all patients, without any other signs of liver injury and drug induced hepatotoxicity. That means, that elevation of these enzymes is benign in the most cases, without any liver pathology. Serdaroglu and co-workers have foud in their study that the most often causes of elevated transaminases in children were infections (34%) and drug-induced liver injury (18.1%), which was associated with slightly elevated transaminases. They also found that elevated transaminases can be detected in completely healthy children (6).

6. CONCLUSION

Valproate may cause the asimptomatic elevation of AST and ALT more friquently than carbamazepine, while carbamazepine may cause the elevation og GGT more frequently than valproate. These elevations are usually benign, without associated liver abnormalities. The most CBZ treated patients develop mild-to-moderate elevations in gamma glutamyltranspeptidase (GGT) levels, probably due to enzyme induction. There were no marked aminotransferase elevations. In our study, there were no cases of hepatotoxicity caused by carbamazepine and valproate.

- Conflict of interest: none declared.
- Authors'contribution: Conception and design:FHC,EH,MM, Acquisition of data: FHC,SZ,SU, Analysis and interpretation of data: FHC,EH,MM,SZ and SU, Drafting the article: FHC, Critically revising the article for important intellectual content: EH, MM and SZ, Approved final version of the article : FHC, EH, MM, SZ and SU

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A. et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014; 55: 475-82. doi: 10.1111/epi.12550
2. Mellish LC, Dunkley C, Ferrie CD, Paul DK. Antiepileptic drug treatment of Rolandic epilepsy and Panayiotopoulos syndrome:Clinical practice survey and clinical tial feasibility. Arch Dis Child. 2015; 100(1): 62-7. doi: 10.1136/archdischild-2013-304211.
3. Djordjevic N, Jankovic SM, Milovanovic JR. Pharmacokinetics and Pharmacogenetics of Carbamazepine in Children. Eur J Drug Metab Pharmacokinet. 2017 Jan 7. doi: 10.1007/s13318-016-0397-3.
4. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, Mattson R, French JA, Perucca E, Tomson T; ILAE Subcommission on AED Guidelines.
5. Update ILAE evidence review of antiepileptic drug efficiacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013 Mar; 54(3): 551-63. doi: 10.1111/epi.12074.
6. Chang R, Chou MC, Hung LY, Wang ME, Hsu MC, Chiu CH. Study of Valproic Acid-Enhanced Hepatocyte Steatosis. Biomed Res Int. 2016; 2016: 9576503. doi: 10.1155/2016/9576503.
7. Serdaroglu F, Koca T, Dereci S, Akcam M. The etiology of hypertransaminasaemia in Turkish children. Bosn J Basic Med Sci. 2016; 6(2): 151-6.
8. Hussein R, Soliman R, Abdelhaleem Ali AM, Tawfeik MH, Abdelrahim M. Effect of antiepileptic drugs on liver enzymes Beni-Suef University Journal of Basic and Applied Sciences. 2013; 2(1): 14-9. doi.org/10.1016/j.bjbas.2013.09.002
9. Ndrepepa G, Kastrati A. Gamma-glutamyl transferase and cardiovascular diseases. Ann Transl Med. 2016; 4(24): 481.doi:10.21037/atm.2016.12.27
10. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: Cause for concern? Epilepsia. 2013 Jan;54(1):11-27. doi: 10.1111/j.1528-1167.2012.03671.
11. Seon Yeong Lee,1 Eunju Sung,2 and Yoosoo Chang3,4 Elevated Serum Gamma-Glutamyltransferase Is a Strong Marker of Insulin Resistance in Obese Children.International Journal of Endocrinology. Volume 2013 (2013), Article ID 578693, 6 pages, http://dx.doi.org/10.1155/2013/578693
12. Hueng-Chuen Fan, Herng-Shen Lee, Kai-Ping Chang.The Impact of Anti-Epileptic Drugs on Growth and Bone Metabolism. Int J Mol Sci. 2016;17(8).pii:E 1242. doi:10.3390/ijms17081242
13. Shokry E, Villanelli F, Malvagia S et al. Therapeutic drug monitoring of carbamazepine and its metabolite in children from dried blood spots using liquid chromatography and tandem mass spectroscopy. J Pharm Biomed Anal 2015; 109:164-70.doi:10.1016/j.jpba.2015.02.045.
14. Berno G, Zaccarelli M, Gori C, Tempestilli M et al. Analysis of single-nucleotide polymorphism (SNPs) in human CYP3A4 and CYP3A5 genes:potential implications for the metabolism of HIV drugs. BMC Med Genet. 2014;15:76. doi: 10.1186/1471-2350-15-76.
15. Jin Sol Lee, Hyun Sub Cheong, Lyoung Hyo Kim, Ji On Kim, Doo Won Seo, Young Hoon Kim, Myeon Woo Chung, Soon Young Han, Hyoung Doo Shin. Screening of Genetic Polymorphisms of CYP3A4 band CYP3A5 genes . Korean J Physiol Pharmacol .2013; 17(6): 479–484. doi: 10.4196/kjpp.2013.17.6.479
16. Yılmaz U, Yılmaz TS, Akıncı G, Korkmaz HA, Tekgül H. The effect of antiepileptic drugs on thyroid function in children Seizure. 2014 Jan; 23(1): 29-35. doi: 10.1016/j.seizure.2013.09.006.
17. Chateauvieux S, Morceau F, Dicato M, Diederich M. Molecular and Therapeutic Potential and Toxicity of Valproic Acid. J Biomed Biotechnol. 2010; 2010: 479364. doi: 10.1155/2010/479364