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The effects of treatment with antiepileptic drugs on serum lipid levels in adult patients with epilepsy

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ABSTRACT

Background: The aim of this study was to evaluate and compare the effects of standard and new antiepileptic drugs on the serum lipid levels of adult patients with epilepsy.

Methods: We retrospectively reviewed the data for 236 adult patients with epilepsy who were receiving standard (old) or modern (new) antiepileptic drugs in monotherapy or polytherapy. The data were collected from the hospital information system of the University Clinical Hospital Mostar for epilepsy patients treated from January 1 to December 31, 2019. The total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) serum levels were analyzed. Statistical Package for the Social Sciences (SPSS) software version 25.0 was used for statistical data analysis, and a comparison of the categorical and continuous variables was undertaken with $\chi 2$. Variables with a p-value of <0.05 were considered statistically significant.

Results: Antiepileptic drugs with the cytochrome P450 (CYP450) enzyme-inducing mechanism, such as phenobarbital, carbamazepine and oxcarbazepine, were not statistically significantly associated with elevated total cholesterol, LDL-C or triglyceride levels. Methylphenobarbital use was statistically significantly linked with raised cholesterol levels ($p=0.033$). Valproate and new generation antiepileptic drugs such as levetiracetam, lamotrigine, pregabalin, and gabapentin, which are not inducers of the CYP450 enzyme, do not affect the total cholesterol, LDL-C or triglyceride serum levels.

Conclusion: The majority of antiepileptic drugs from the group of CYP450 enzyme-inducers do not increase the total cholesterol, LDL-C, or triglyceride levels in patients with epilepsy. However, methylphenobarbital use causes an increase in total cholesterol levels. New generation antiepileptics do not affect the total cholesterol, LDL-C, or triglyceride serum levels.

Key words: cholesterol, LDL-C, triglycerides, antiepileptic drugs

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INTRODUCTION

Epilepsy is the most common chronic neurological disease, and due to its frequency and characteristics, it is a serious medical and social problem. It is estimated that 65 million people worldwide suffer from epilepsy, with 80% of these living in developing countries (1). The prevalence of epilepsy is 6.4 per 1000 inhabitants and increases with age, with a peak in the oldest age groups and socially deprived societies. The incidence of epilepsy is 61.4 per 100,000 people per year (2).

Antiepileptic drugs are the basis of treatment for the majority of patients with epilepsy. The main goal of treatment is good control or the complete reduction of seizures at the lowest effective and tolerated dose. When choosing an appropriate antiepileptic therapy, some of the recommendations that have to be followed include defining the type of epilepsy or epileptic syndrome, starting appropriate antiepileptic therapy in the optimal dose as early as possible, and taking care of specific population groups with regard to physiological specificities, comorbidities, and the pharmacokinetic and pharmacodynamic properties of drugs, as well as additional therapy and possible interactions with antiepileptics (3).

Antiepileptics can be divided into two groups. The classic antiepileptic drugs (also known as the main, conventional or old ones) are phenobarbital (PB), methylphenobarbital (MPB), phenytoin (PHT), acetazolamide (ACT), primidone (PRM), ethosuximide (ESC), sulthiame (SUL), carbamazepine (CBZ), valproate (VPA), clonazepam (CNZ), clobazam (CLB) and piracetam (PCT). For the last 20 years, more new medicines have been approved for the treatment of epilepsy than in any other neurological area (7). The new generation of antiepileptics includes vigabatrin (VGB), lamotrigine (LTG), gabapentin (GBP), felbamate (FBM), topiramate (TPM), tiagabine (TGB), fosphenytoin (fPHT), oxcarbazepine (OXC), levetiracetam (LEV), pregabalin (PGB), zonisamide (ZNS), rufinamide (RUF), stiripentol (STP), lacosamide (LCS), eslicarbazepine acetate (ESL), retigabine (RTG), perampanel (PER) and brivaracetam (BRV). Since the latter antiepileptics came into use after 1989, the term "modern antiepileptics" has recently been used (4).

Classic "old" antiepileptics are very effective, but they are now being used less often because of the high risk of serious side effects. Most modern antiepileptics have the same effectiveness as the classic ones, but a significantly lower risk of serious side effects and fewer interactions with other drugs, meaning that their use is preferred nowadays (5).

Epilepsy requires long-term and sometimes lifelong therapy, and prolonged treatment with antiepileptic drugs could therefore have certain side effects (6). Several studies have shown that frequently used antiepileptics such as phenytoin, phenobarbital and carbamazepine can increase serum lipid levels, while on the other hand valproate and other newer antiepileptics such as lamotrigine and levetiracetam do not have such an effect (7).

Since most of the anticonvulsive drugs induce hepatic cytochrome P450 (CYP450) enzymes, competition between the drug and serum lipids for this enzyme is thought to occur, resulting in the reduced breakdown of cholesterol into bile acids and an increase in the total serum cholesterol level (8).

It is important to emphasize that epilepsy is a chronic disease that often begins at a young age, as well as that elevated concentrations of serum lipids in young adults can represent an important risk factor for the development of cardiovascular and cerebrovascular diseases later in life (9). The observation of changes in serum lipid levels after the introduction of antiepileptic therapy can thus be a useful method for choosing the safest drug aimed at the long-term prevention of cardiovascular and

cerebrovascular diseases for patients with epilepsy (10).

The aim of this research is to evaluate and compare the effects of standard or old (phenobarbital, phenytoin, ethosuximide, carbamazepine, valproate, clonazepam, clobazam) and modern or new (lamotrigine, gabapentin, topiramate, oxcarbazepine, levetiracetam, pregabalin) antiepileptic drugs on serum lipid levels in adult patients with epilepsy from Herzegovina area (Bosnia and Herzegovina) treated at the University Clinical Hospital Mostar.

PARTICIPANTS AND METHODS

Subjects

A total of 236 subjects diagnosed with epilepsy with available blood data about their serum lipid status and total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride serum levels took part in this research. The subjects were adult patients with a diagnosis of epilepsy who were receiving therapy with standard/old or new/modern antiepileptic drugs followed through the epilepsy outpatient clinic at the University Clinical Hospital Mostar.

The criteria for inclusion included patients with a diagnosis of epilepsy older than 18 years, males and females, visiting the epilepsy outpatient clinic, who were taking standard/old or new/modern antiepileptic drugs with available data on serum lipid values. The exclusion criteria encompassed patients with a diagnosis of epilepsy on antiepileptic drugs for whom we did not have data on the levels of serum lipids, those on combined therapy with standard and new antiepileptic drugs and those who did not have complete documentation.

Methods

The research was conducted at the Clinic of Neurology, University Clinical Hospital Mostar. The data were taken from the hospital information system of the University Clinical Hospital Mostar and included patients treated through the epilepsy outpatient clinic in the period from January 1, 2019, to December 31, 2019.

Socio-demographic characteristics such as age and gender, data about antiepileptic therapy, and the results of biochemical analyses such as values of total cholesterol, LDL-C and triglycerides were collected. We analyzed the influence of standard antiepileptics compared to that of newer ones on the total levels of serum lipids.

The research and all protocols were approved by the Ethics Committee of the Faculty of Medicine of the University of Mostar. All procedures performed were in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki (11).

Statistical analysis

The statistical analysis was calculated with IBM Statistical Package for the Social Sciences (SPSS) Statistics, version 25.0. (Armonk, NY: IBM Corp.). The results were expressed as numbers and percentages. The chi-square test was utilized to test the significant difference between the parameters, and Fisher's exact test was used when the expected frequency was less than 5. The limits of statistical significance were set at $p<0.05$. P-values that could not be expressed to three decimal places were expressed as $p<0.001$.

RESULTS

Of all the drugs included in our study, only methylphenobarbital led to a statistically significant elevation of cholesterol values, and there were no statistically significant differences in the effects of other drugs in terms of causing elevated cholesterol values in our patients with epilepsy (Table 1).

There were no statistically significant differences in the effects of antiepileptic drugs in terms of causing elevated LDL-C values in our patients with epilepsy (Table 2).

Table 1. Differences in total cholesterol levels

	Elevated total cholesterol values				χ^2	p
	No		Yes			
	n	%	n	%		
Carbamazepine	38	92,7	174	89,2	0,145	0,776*
Oxcarbazepine	32	78,0	151	77,4	0	1
Levetiracetam	30	73,2	126	64,6	0,758	0,384
Valproate	28	68,3	117	60,0	0,664	0,415
Phenobarbital	38	92,7	185	94,9	0,033	0,704*
Methylphenobarbital	37	90,2	191	97,9	4,014	**0,033***
Lamotrigine	21	51,2	115	59,0	0,547	0,460
Clobazam	40	97,6	185	94,9	0,112	0,695
Pregabalin	39	95,1	194	99,5	2,253	0,079*
Gabapentin	41	100,0	193	99,0	0	1*
Topiramate	40	97,6	184	94,4	0,209	0,697*
Clonazepam	40	97,6	185	94,9	0,112	0,695*
Ethosuximide	41	100,0	192	98,5	0,001	1*

*Fisher's exact test

There were also no statistically significant differences in the effect of antiepileptic drugs in terms of causing elevated triglyceride values in our patients with epilepsy (Table 3).

Table 2. Differences in LDL-C levels

	Elevated LDL-C values				χ^2	p
	No		Yes			
	n	%	n	%		
Carbamazepine	11	100,0	201	89,3	0,339	0,609*
Oxcarbazepine	9	81,8	174	77,3	0	1*
Levetiracetam	7	63,6	149	66,2	0	1*
Valproate	9	81,8	136	60,4	1,221	0,211*
Phenobarbital	10	90,9	213	94,7	0	1*
Methylphenobarbital	11	100,0	217	96,4	0	1*
Lamotrigine	3	27,3	133	59,1	3,147	0,057*
Clobazam	10	90,9	215	95,6	0	1*
Pregabalin	11	100,0	222	98,7	0	1*
Gabapentin	11	100,0	223	99,1	0	1*
Topiramate	11	100,0	213	94,7	0,007	1*
Clonazepam	11	100,0	214	95,1	0	1*
Ethosuximide	11	100,0	222	98,7	0	1*

*Fisher's exact test

Table 3. Differences in triglyceride levels

	Elevated triglyceride levels				χ^2	p
	No		Yes			
	n	%	n	%		
Carbamazepine	24	88,9	188	90,0	0	0,774*
Oxcarbazepine	19	70,4	164	78,5	0,496	1,481
Levetiracetam	20	74,1	136	65,1	0,510	1,475
Valproate	16	59,3	129	61,7	0,001	0,970
Phenobarbital	25	92,6	198	94,7	0	0,649*
Methylphenobarbital	24	88,9	204	97,6	3,207	0,051*
Lamotrigine	19	70,4	117	56,0	1,481	0,214*
Clobazam	26	96,3	199	95,2	0	1*
Pregabalin	27	100,0	206	98,6	0	1*
Gabapentin	27	100,0	207	99,0	0	1*
Topiramate	27	100,0	197	94,3	0,660	0,370*
Clonazepam	27	100,0	198	94,7	0,541	0,620*
Ethosuximide	27	100,0	206	98,6	0	1*

* Fisher's exact test

DISCUSSION

We did not observe a statistically significant increase in the levels of total cholesterol, LDL-C and triglycerides in our population of patients with epilepsy treated with phenobarbital, while in those treated with methylphenobarbital, we found a statistically significant increase in total cholesterol values. The results obtained in this paper did not completely coincide with the results of some other works. Studies conducted by Kumar et al. and Manimekalai et al. reported a rise in total cholesterol, LDL-C and triglyceride levels in patients with epilepsy who were on long-term therapy with methylphenobarbital, as well as in ones who were on long-term therapy with phenobarbital (7, 12). One of the possible explanations for such results could be the fact that our patients receiving antiepileptic therapy are mostly younger (with an average age of 33 years), which may be the reason for the normal lipid values. In the majority of investigations in which there was a growth in the value of serum lipids in patients taking phenobarbital, the average age was 48 or more, and we know that the risk of higher serum lipid levels rises with age. Another explanation could be that our patients were not on high doses of phenobarbital, because the induction of liver enzymes and the increment in lipid levels depend on the dose of the drug, so with lower doses there is a smaller risk of elevating cholesterol and triglyceride levels.

In addition, no effect was observed regarding the levels of total cholesterol, LDL-C and triglycerides in our patients with epilepsy treated with carbamazepine and oxcarbazepine. On the other hand, some previous investigations have shown that in patients treated with carbamazepine there was a significant increase in the levels of triglycerides and LDL-C (13, 14). However, there are also some studies that did not demonstrate a statistically significant rise in average lipid values in those patients, like the results obtained by Yis et al. (15) in their research.

The effect of phenobarbital, methylphenobarbital and carbamazepine may be due to the induction of CYP enzymes, more specifically CYP51 enzymes. CYP51 is a gene mediating the synthesis of ergosterol from the cytochrome P450 super family, which is

involved in the biosynthesis and metabolism of cholesterol in humans (16).

Epilepsy patients on valproate and levetiracetam did not show statistically significant changes in total cholesterol, LDL-C and triglyceride levels. Not enough data are available on the relationship between lipid function and levetiracetam. However, since levetiracetam and valproate have no significant influence on lipid metabolism, this suggests that neither drug is an inducer of the CYP51 enzyme (7).

In patients with epilepsy treated with newer antiepileptic drugs such as lamotrigine, pregabalin, gabapentin and topiramate, no statistically significant increase in the average values of serum lipids was demonstrated. This suggests that the metabolism of these drugs mostly goes through the glucuronidation process, and not through the induction of the CYP51 enzyme. These drugs therefore avoid competition with cholesterol for the CYP51 enzyme, meaning that there is no rise in the level of serum lipids (5).

It should be pointed out that the obtained results do not completely match the outcomes of similar research. Possible reasons for this discrepancy may be the differences in sample size, study approaches such as variations in the patient selection criteria and types of antiepileptic drugs utilized by the patients, as well as the variance in socio-economic status.

Our research has some limitations, such as the small sample size. Therefore, for a better understanding, a more detailed cross-sectional clinical study on the serial monitoring of changes in serum lipid levels from the start of antiepileptic therapy through the whole period of drug taking is needed to confirm the results obtained.

One strength of this study is that it is the first to attempt to determine the effects of antiepileptic drugs on serum lipid levels among epilepsy patients in Bosnia and Herzegovina, hence ultimately adding to the limited data.

The observation of changes in serum lipid levels after the initiation of antiepileptic therapy would be a useful method for selecting the safest drug for patients with epilepsy. This research, although limited in scope, is still a good basis for future investigations.

CONCLUSION

The majority of antiepileptic drugs from the group of CYP450 enzyme-inducers do not increase total cholesterol, LDL-C, and triglyceride levels in our patients with epilepsy. However, methylphenobarbital use causes an increase in total cholesterol levels. New generation antiepileptics do not affect total cholesterol, LDL-C, or triglyceride serum levels.

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CONFLICT OF INTEREST

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHORS' CONTRIBUTIONS

NPS: contribution to study conception and design, literature review, supervision, writing the paper, interpretation of data, critical revision of the paper; IH: acquisition of data, literature review, critical revision of the paper; NP: literature review, critical revision of the paper, assistance in writing the paper; MB: literature review, assistance in writing the paper

ETHICAL BACKGROUND

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: We deny any restrictions on the availability of data, materials and associated protocols. Derived data supporting the findings of this study are available from the corresponding author on request.

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