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Are the Effects of Old and New-Generation Antiepileptic Drugs on Hemogram Parameters Different?

Eski ve Yeni Kuşak Antiepileptik İlaçların Hemogram Parametrelerine Etkileri Farklı Mı?

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Abstract

Introduction: There are different comments related to hematological side effects caused by antiepileptic drugs (AEDs). In our study, we investigated the effects of AEDs on hemogram parameters.

Material and Method: Hemogram values of 293 patients including 156 women, who used AEDs for at least six months, were compared with the values of 36 healthy control participants group who did not. In addition, the hemogram values of the patients using old-generation AEDs such as phenytoin (PHT), carbamazepine (CBZ), valproic acid were compared with those using new-generation AEDs as levetiracetam, oxcarbazepine, pregabalin (PGB), gabapentin and two AEDs in combination.

Results: Comparison of the patients using AEDs with the control group revealed that white blood cell (WBC) values of only PHT users were lower than the control group (p=0.045). Red cell distribution width (RDW) values were found to be higher in healthy controls than those using AEDs (p<0.001). When the groups using AEDs were compared among themselves, it was found that the WBC values of the users of old- generation AEDs as PHT and CBZ were significantly lower than those using PGB (p=0.006; P=0.005, respectively).

Conclusions: As hematological side effects, AEDs may decrease WBC counts. The WBC decreasing effects of PHT and CBZ, which are older generation antiepileptics, are more pronounced than pregabalin, which is a new-generation AED. The effects of AEDs on hemogram parameters of the patients should be taken into consideration while choosing appropriate AEDs and also while following the patient.

Keywords: Antiepileptic drugs, hemogram, white blood cells, RDW

Öz

Amaç: Antiepileptik ilaçların (AEİ) neden oldukları hematolojik yan etkilerle ilişkili farklı sonuçlar vardır. Çalışmamızda AEİ'ların hemogram parametrelerine olan etkilerini araştırdık.

Gereç ve Yöntem: En az altı ay AEİ kullanan 156'sı kadın 293 hastanın hemogram değerleri AEİ kullanmayan 36 sağlıklı kontrol grubunun değerleri ile karşılaştırıldı. Ayrıca AEİ olarak eski kuşak antiepileptik ilaçlardan fenitoin (PHT), karbamazepin (KBZ), valproik asit, daha yeni kuşak antiepileptik ilaçlardan levetirasetam, okskarbazepin, pregabalin (PGB), gabapentin ve ikili AEİ kullanan hastaların hemogram değerleri birbirleri ile karşılaştırıldı.

Bulgular: AEİ kullanan hastaların kontrol grubu ile karşılaştırmalarında sadece PHT kullananların beyaz kan hücre değerleri kontrol grubuna göre düşük bulundu (p=0.045). Sağlıklı kontrollerde "red cell distribution width" (RDW) değeri AEİ kullananlara göre daha yüksek bulundu (p<0.001). AEİ kullanan gruplar kendi aralarında karşılaştırıldığında eski kuşak AEİ'lardan olan PHT ve KBZ kullananların PGB kullananlara göre beyaz kan hücre değerlerinde anlamlı düşüklük tespit edildi (sırasıyla p=0.006; P=0.005).

Sonuç: AEİ'lar hastalarda hematolojik yan etki olarak özellikle beyaz kan hücre düşüklüğüne neden olabilirler. Daha eski kuşak AEİ'lardan olan PHT ve KBZ'in yeni kuşak AEİ'lardan pregabaline göre beyaz kan hücre değerlerinde azalma yapıcı etkileri daha belirgindir. Hastalar için ilaç seçimi yapılırken ve takipleri süresince AEİ'ların hemogram parametreleri üzerine etkileri göz önüne alınmalıdır.

Anahtar sözcükler: Antiepileptik ilaçlar, hemogram, beyaz kan hücreleri, RDW

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INTRODUCTION

Antiepileptic drugs (AEDs) play an important role in controlling seizures and increasing the quality of life of patients with epilepsy. AEDs are also used for a long time in cases such as neuropathic pain, movement disorders, psychiatric diseases. Therefore, it is important to monitor closely their clinical and biochemical side effects. As is known, AEDs can have hematological side effects.[1] It has been reported that they may cause many side effects such as thrombocytopenia, leukopenia, neutropenia, pancytopenia, pure red cell aplasia, aplastic anemia, macrocytosis, megaloblastic anemia, and bone marrow depression.[2,3] However, data on which AEDs have more of these side effects differ. Although AEDs have been reported to cause thrombocytopenia and a decrease in white blood cells, leukocytosis has been reported in some case reports.[4] Hematological effects are more common in patients who use more than one antiepileptic drug (AED).[3] In the hemograms of the patients, white blood cell (WBC), red blood cell (RBC), and platelet (PLT) counts; hemoglobin (HB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)), red blood cell distribution width (RDW), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW) values are important for monitoring the hematological effects of the drugs. Changes in these blood parameters may sometimes convey vital importance. Limited number of studies have been performed on hematological side effects of AEDs. In our study, we examined the changes in hemogram parameters of patients using AEDs.

MATERIAL AND METHOD

Ethics committee approval was obtained for the study (Yıldırım Beyazıt University Faculty of Medicine Non-Pharmaceutical Clinical Research Ethics Committee. No: 09, Date: 11.06.2012). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who had been using only AEDs for at least six months, and older than 18 years of age without known any oncological, rheumatological, immunological, hematological, allergic, infectious and granulomatous diseases; metabolic disease other than diabetic polyneuropathy, and bleeding diathesis were included in this retrospective study. A total of 293 patients using AEDs, including 156 women, were included in the study. The average age of the patient population was 42 (range 18-88) years. The control group consisted of 36 healthy volunteers who did not use AEDs. The study population consisted of patients using valproic acid (VPA) (n=97), levetiracetam (LEV) (n=29), oxcarbazepine (OXC) (n=14), phenytoin (PHT) (n=12), carbamazepine (CBZ) (n=37), pregabalin (PGB) (n=40), gabapentin (GBP) (n=34), other AEDs (n=9) and two AEDs in combination (n=21). The control group consisted of healthy individuals who did not use any antiepileptics or any other drugs. WBC, RBC, HB, HCT, MCV, MCH, MCHC, RDW, PLT, MPV, PCT, PDW values detected in the final control hemograms performed when the patients came to the neurology outpatient clinic were recorded.

All data were processed using Microsoft Excel for Windows and SPSS programs. Patients' gender, age, hematological parameters, and AEDs used were recorded as variables. Means, ranges, frequencies, and ratios were used for descriptive statistics and assessments of categorical variables. One-way analysis of variance (Anova) was used for the relationship of AEDs with hematological data, and Tukey post-hoc test was used for paired comparisons. The effect of age and gender was investigated with Bonferroni test. The value of $p < 0.05$ was accepted for statistical significance.

RESULTS

When the hemogram parameters (WBC, RBC, HB, HCT, MCV, MCH, MCHC, RDW, PLT, MPV, PCT, PDW) were compared in patients using any AED with those in the control group not using AEDs, a statistically significant difference between only WBC counts ($p < 0.001$) and RDW values ($p < 0.001$) was detected. When paired comparisons of WBC counts were made between the control group and the each group using AEDs separately, the significant difference was found only between the patients in the control group and those using PHT ($p=0.045$) (**Table 1**). When paired comparisons of RDW measurements between the control group and the groups using AEDs were made, a significant difference was detected for each drug group ($p < 0.001$) (**Table 2**). This significant difference did not change when Bonferroni corrections were calculated for the parameters of age and gender. When the patient groups using AEDs were compared among themselves in terms of hemogram parameters, only WBC values were found to be significantly different ($p < 0.001$) (**Table 3**). In paired comparisons between groups, this difference was found to be between PGB and PHT ($p=0.006$) and between PGB and CBZ ($p=0.005$) (**Table 4**). In these comparisons, when Bonferroni corrections were made for age and gender, the significance of this difference further increased. However, the risk of decrease in white blood cell counts did not increase with the use of two AEDs in combination ($p > 0.05$).

Table 1. Comparisons between groups that used and did not use AEDs in terms of WBC counts

	N	Mean ±SD	P value*
Control	36	7.40±2.15	
VPA	97	6.62±1.57	0.525
LEV	29	7.08±2.41	1.000
OXC	14	6.07±1.68	0.441
PHT	12	5.36±1.40	0.045**
CBZ	37	6.07±1.70	0.086
PGB	40	7.70±1.87	1.000
GBP	34	6.53±1.54	0.662
Dual AEDs	21	6.82±2.29	0.984

*Comparison with the control group, Valproic acid (VPA), levetiracetam (LEV), oxcarbazepine (OXC), phenytoin (PHT), carbamazepine (CBZ), pregabalin (PGB), gabapentin (GBP), antiepileptic drugs (AEDs), standart deviation (SD), white blood cell (WBC).

Table 2. Comparisons between groups that used and did not use AEDs in terms of RDW values

	N	Mean ±SD	P value*
Control	36	36.65±10.73	-
VPA	97	15.14±6.96	<0.001
LEV	29	16.50±9.32	<0.001
OXC	14	13.44±1.08	<0.001
PHT	12	13.19±1.12	<0.001
CBZ	37	15.37±8.34	<0.001
PGB	40	15.27±6.06	<0.001
GBP	34	13.89±1.01	<0.001
Dual AEDs	21	16.27±9.41	<0.001

Comparison with the control group, Valproic acid (VPA), levetiracetam (LEV), oxcarbazepine (OXC), phenytoin (PHT), carbamazepine (CBZ), pregabalin (PGB), gabapentin (GBP), antiepileptic drugs (AEDs), standart deviation (SD), red cell distribution width (RDW).

Table 3. Comparisons of hemogram parameters among AED users (Anova) (n=284 patients

	Mean±SD	p-value
WBC	6.73±1.95	<0.001**
RBC	6.50±28.71	0.492
HB	13.95±1.60	0.330
HCT	41.50±4.18	0.240
MCV	87.32±6.35	0.420
MCH	29.45±2.63	0.060
MCHC	33.62±1.42	0.052
RDW	15.06±6.71	0.737
PLT	231.38±68.74	0.207
MPV	10.88±6.66	0.930
PCT	0.25±0.07	0.376
PDW	13.38±2.31	0.174

*Patients using other AEDs were not included in the analysis. **Statistically significant. Antiepileptic drugs (AEDs), standart deviation (SD), white blood cell (WBC), red blood cell (RBC), platelet (PLT), hemoglobin (HB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)), red blood cell distribution width (RDW), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW).

DISCUSSION

In our study, we examined whether there were any changes in the hemogram parameters of patients using AEDs. When the group using any AED was evaluated with the control group, the WBC counts of those using AEDs were found to be lower than the control group. When the groups using AEDs were compared with the control group, it was seen that this difference was caused by the group using PHT. When AEDs were compared among themselves, WBC counts significantly decreased in patients using PHT and CBZ, which are old-generation AEDs, compared to patients using PGB, which is a new AED.

It has been stated that the hematological side effects of AEDs may range from thrombocytopenia to neutropenia, anemia, red cell aplasia, and bone marrow failure.[5,6] In some studies, it has been reported that old-generation AEDs such as CBZ, PHT, phenobarbital, VPA induce frequent hematological changes when compared with new-generation AEDs (such as PGB, GBP, LEV, LTG, OXC, TPM, ZA), comparable to our results.[5]

The causes of hematological side effects of AEDs have not been fully understood, yet. These effects may be related to many different mechanisms such as direct toxic effects of the drugs on bone marrow, increased levels of toxic metabolites, and homocysteine, decrease in folic acid levels, direct effects of drugs on cells or their immunological effects. Neutropenia due to AEDs usually occurs in the first weeks after exposure to the drug and resolves within the first days after the drug is discontinued.[5] It is known that CBZ can cause moderate leukopenia, eosinophilia, and rarely leukocytosis.[7] Patients with low leukocyte or neutrophil counts prior to CBZ treatment may experience transient leukopenia and less frequently neutropenia.[5] Neutropenia is a rare side effect of GBP therapy.[5] Leukopenia, neutropenia, and pancytopenia have been described with LEV.[5] PHT can cause thrombocytopenia, leukopenia, neutropenia, pancytopenia, pure red cell aplasia, aplastic anemia, macrocytosis, and megaloblastic anemia.[5] Monotherapy or combination therapies with CBZ, PHT, phenobarbital and VPA decrease platelet counts more significantly when compared to treatments with newer

Table 4. Comparisons of AEDs among themselves as for their effects on WBC counts (Tukey test)

Drugs	WBC mean±SD	p-value							
		VPA	LEV	OXC	PHT	CBZ	PGB	GBP	Dual- AEDs
VPA (n=97)	6.62±1.57	-	0.95	0.882	0.405	0.842	0.060	1.000	1.000
LEV (n=29)	7.09±2.41		-	0.754	0.151	0.401	0.925	0.958	1.000
OXC (n=14)	6.07±1.67			-	0.989	1.000	0.119	0.997	0.962
PHT (n=12)	5.35±1.40				-	0.967	0.006*	0.635	0.430
CBZ (n=37)	6.06±1.70					-	0.005*	0.981	0.864
PGB (n=40)	7.70±1.87						-	0.164	0.728
GBP (n=34)	6.53±1.54							-	1.000
Dual –AEDs (n=21)	6.82±2.29								-

Valproic acid (VPA), levetiracetam (LEV), oxcarbazepine (OXC), phenytoin (PHT), carbamazepine (CBZ), pregabalin (PGB), gabapentin (GBP), antiepileptic drugs (AEDs), standart deviation (SD), white blood cell (WBC).

AED combinations.[8,9] Thrombocytopenia observed in some patients using CBZ or OXC has been attributed to excessive destruction of peripheral blood platelets.[10] It has been shown that the mechanism of thrombocytopenia is not directly related to the toxicity of CBZ, OXC or their metabolites.[10] Routine monitoring of platelet counts is recommended in patients treated with CBZ and OXC.[10] VPA may cause cytopenia by directly affecting the bone marrow or acting on one or more cell lines (pancytopenia, neutropenia, leukopenia).[11,5] The effects of VPA on the normal hematopoietic system are still largely unknown. It has been reported that in vitro VPA treatment affects the composition of hematopoietic progenitor cells, myeloid progenitor compartment, resulting in a significant and concentration-dependent inhibition of neutrophil differentiation.[12] VPA can change the membrane matrix by affecting the sphingomyelin and phosphotidylserine content in erythrocytes.[13] It has been reported that there is an increase in MCV and MCH values in patients who received VPA as mono or polytherapy.[14] Most frequently VPA induces thrombocytopenia.[15,16] Available data report a prevalence of thrombocytopenia between 5% and 54% of patients treated with VPA (12-18% in studies with sample size > 150). The risk of thrombocytopenia increases in elderly female patients, especially those who receive VPA above a dose of 1g/day.[17] The mean age of our patients using VPA was 34.2±15.8 years. In one study, when hematological changes were compared in patients treated with VPA, CBZ, LEV, and LTG, lower platelet counts were found in those treated with LEV monotherapy compared to healthy controls, and no difference was detected in HB and WBC values.[1] In our study, we did not find decreased platelet counts in patients using VPA, LEV and other AEDs. Megaloblastic anemia has been reported as potential side effect of PHT.[18] In one study leukopenia and lymphopenia were detected n PHT users, and in this study an inverse correlation was found between serum folate and PHT levels which was directly attributed to the toxic effects of the drug.[19] PHT monotherapy in children with epilepsy can significantly increase serum homocysteine levels and cause a significant decrease in serum folate and vitamin B12 levels.[20,21] Contrary to these data, some researchers reported that AEDs do not have a significant effect on biochemical and hematological parameters of epileptic patients.[22]

In our study, we found that the WBC counts were lower in patients using the old- generation AEDs especially PHT and CBZ compared to those using PGB which is one of the new-generation AEDs. In addition, we could not find any reduction in white blood cell counts in patients using two AEDs. We found no difference in the PLT, RBC, HB, HCT, MCV, MCH, MCHC, RDW, MPV, PCT, PDW values of our patients depending on the AEDs they used. In our study, RDW values of the healthy group were higher than those using AEDs, compared to the control group, while the RDW values did not differ among AED users. RDW is an index that measures the heterogeneity in the dimensions of erythrocytes.[23] As a simple and inexpensive test, RDW provides valuable information about general health status, different diseases, clinical results, complications, and mortality regardless of the underlying disorder.[24]

The shortcomings of our study can be specified as the low number of patients enrolled in the study groups for each drug; the failure to perform peripheral smear; the absence of the levels of blood AED concentrations, blood iron, ferritin, iron binding capacity, sedimentation, CRP, homocysteine, folic acid and vitamin B12; and also the absence of the counts of leukocytes' subtypes.

CONCLUSION

In conclusion, as a hematological side effect, AEDs may decrease WBC counts. The effects of PHT and CBZ, which are among the old-generation AEDs, on WBC counts are more pronounced than PGB, which is one of the new-generation AEDs. It is important to check and monitor the hemogram parameters while selecting AEDs for patients and also in the follow-up of patients using these drugs.

The effects of antiepileptic drugs on hematological parameters are still controversial. In particular, the WBC profiles of patients using old-generation antiepileptic drugs should be followed more closely..

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained for the study (Yıldırım Beyazıt University Faculty of Medicine Non-Pharmaceutical Clinical Research Ethics Committee. No: 09, Date: 11.06.2012).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Bachmann T, Bertheussen KH, Svalheim S, Rauchenzauner M, Luef G, Gjerstad L, Taubøll E. Haematological side effects of antiepileptic drug treatment in patients with epilepsy Acta Neurol Scand Suppl 2011;19123-7.
2. O'Connor CR, Schraeder PL, Kurland AH, O'Connor WH. Evaluation of the mechanisms of antiepileptic drug-related chronic leukopenia Epilepsia Jan-Feb 1994;35(1):149-54.
3. Ramsay RE. Use of Phenytoin and carbamazepine in the treatment of epilepsy. Neurologic ClinicsVolume 1986;4(3):585-600.
4. Murphy JE, Stewart RB, Springer PK. Carbamazepine-induced leukocytosis. Am J Hosp Pharm1980;37(4):550-2.

5. Verrotti A , Scaparrotta A, Grosso S, Chiarelli F, Coppola G. Anticonvulsant drugs and hematological disease. Neurol Sci 2014;35(7):983-93.
6. Özkaya H, Aydemir G, Akcan AB, et al. Carbamazepine-induced Red Blood Cell Aplasia: A Case Report. Turk J Hematol. 2012;29(2): 195-196.
7. Hart R G, Easton JD. Carbamazepine and hematological monitoring. Ann Neurol 1982;11(3):309-12.
8. Aliyu H, Ayo JO,Ambali S, et al. Heamatobiochemical Alterations Induced by Carbamazepine and Phenytoin: Mini Review. Biochem Pharmacol (Los Angeles) 2016;5:5.
9. Bhosale UA, Loharkar NR, Yegnanarayan R,Quraishi N. Study of effects of antiepileptic therapy on various biochemical and hematological parameters patients suffering of epilepsy. Int J Basic Clin Pharmacol 2014;3(1):79-85.
10. Tutor-Crespo MJ, Hermida J, Tutor JC. Relation of blood platelet count during carbamazepine and oxcarbazepine treatment with daily dose, and serum concentrations of carbamazepine, carbamazepine-10, 11-epoxide, and 10-hydroxycarbazepine. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2007;151(1):91-4.
11. Handoko KB, Souverein PC, Van Staa TP, et al. Risk of aplastic anemia in patients using antiepileptic drugs. Epilepsia 2006;47(7):1232-6.
12. Bartels M, Geest CR, Bierings M, Buitenhuis M, Coffer PJ. Histone deacetylase inhibition modulates cell fate decisions during myeloid differentiation. Haematologica 2010;95(7):1052-60.
13. Davıs RG, Sunder T, Barakat HA, May R. Valproate alters the membrane phospholipids of erythrocytes. Epilepsia 1991;32(suppl 3);11-12.
14. Ozkara C, Dreifuss FE, Apperson Hansen C. Changes in red blood cells with valproate therapy. Acta Neurol Scand 1993;88(3):210-2.
15. Allan RW. Myelodysplastic syndrome associated with chronic valproic acid therapy: a case report and review of the literature. Hematology 2007;12:493–6.
16. Acharya S, Bussel J. Hematologic toxicity of Sodium Valproate. J Pediatr Hematol Oncol 2000;22:62–5.
17. Mori F, Caffarelli C, Caimmi S, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) in children. Acta Biomed 2019;90(Suppl 3):66-79.
18. Weber TH, Knuutila S, Tammisto P, Tontti K. Long-term of phenytoin: Effects on whole blood and red cell folate and haematological parameters. Scand J Haematol 1977;18(2):81-5.
19. Diago MP, Rodríguez MAA, Giner AA, Sirvent MLP. [Hematologic alterations and reduction in serum folate in epileptics treated with anticonvulsants]. Neurologia1989;4(4):119-23.
20. Sharma TK, Vardey S K, Sitaraman S. Homocysteine Metabolism and Hematological Parameters in Early Stage of Phenytoin Treated Epileptic Children. Clin Lab 2017;63(7):1089-1097.
21. Dinç D, Schulte PFJ. [The use of anticonvulsants and the levels of folate, vitamin B12 and homocysteine].Tijdschr Psychiatr 2018;60(1):20-28.
22. Pee DH, Park YK, Eun BL, Park SH, Kim SK. The Hematologic Effect of Antiepileptic Drug. J Korean Pediatr Soc 1997;40(2):217-224.
23. Evans TC, Jehle D. The red blood cell distribution width. J Emerg Med 1991;9(Suppl 1):71-4.
24. Yousefi B, Sanaie S, Ghamari AA, Soleimanpour H, Karimian A, Mahmoodpoor A. Red cell distribution width as a novel prognostic marker in multiple clinical studies. Indian J Crit Care Med 2020;24(1):49-54.