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Prevalence of Side Effects Treatment with Carbamazepine and Other Antiepileptics in Patients with Epilepsy

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ABSTRACT

Objective: This paper reveals the studies of carbamazepine monitoring in the manifestation of side effects during clinical use. It is important to realize that these ranges are derived statistically, with most patients who have high levels suffering side effects and some with poor control having low levels. Broadly, the newer agents have advantages of lower risk of side effects and less drug interaction. At the presence they are more expensive than the, than "older" agents. Current recommendations and practice are to use newer agents as second line drugs, although in some countries there are gaining favour as potential first line agents. **Methods:** In the study 91 patients with epilepsy were involved from which 53 or 58.2% were female and 38 or 41.8% were male with no great significant difference between two genders (X^2=2.47, *P*=0.116). However, according to the study results female patients had slightly greater prevalence of epilepsy than man. Average age of epileptic patients was 23.2 years (SD ± 16.4 years), in the range 1–66 years. Patient distribution was present within all age-groups, but 59.4% of all patients were up to 20 years old. The highest prevalence of epilepsy was in the group age 6-15 years old: 33.0%. There were also children 1 – 5 years old with 7 or 7.7% of the patients, and the patients older than 60 years with 4 or 4.4% of the patients. Patient distribution according to the age and gender results with no female patient over 60 year old and more female patients in the age group 1-5 years. However statistically this did not produce a highly significant difference (T-test= 0.72, *P*=0.437) between average age according to the gender. The average age of the female gender was 22.1 year (SD ± 14.2 years), with the range 2-55 years, while the average age of the male patients was 24.6 year (SD ±19.2 years), with the range 1-66 years. **Conclusion:** Unwanted side effects of antiepileptic drugs analyzed in the study are frequent, but not so severe as to be life threatening. Treatment of epilepsy with these three drugs (carbamazepine, ac.valproic and phenobarbitone) would be the first choice of treatment, with the best safety and efficacy. Application of this therapy is rarely compromised because of the appearance of unwanted side effects. Replacement or termination of therapy may be applied if actual therapy is not adequate for the management of epileptic attacks.

Key words: Carbamazepine, antiepileptics, side effects.

1. INTRODUCTION

Epilepsy is one of the most common neurologic problems worldwide. It is also the second most common chronic neurological condition seen by neurologists (1). In recent years, important advances have been made in the diagnosis and treatment of seizure disorders (2).

Epilepsy syndrome can be also classified according to the type of seizure, the presence or absence of neurologic or developmental abnormalities and electroencephalographic (EEG) findings (3). For example, the syndrome of juvenile myoclonic epilepsy is characterized by the onset of myoclonic seizures, generalized tonic-clonic seizures, and less frequently absence seizures in adolescents who have normal intellectual function, with EEG findings of rapid, generalized spike-wave and polyspike-wave discharges (4). In epilepsy, a common problem is diagnostic accuracy as it can be diagnose only by taking a history of the index event or by chance observation of a seizure (5). As many as 10%-20% of cases referred to specialized epilepsy units with seemingly intractable seizures do not have epilepsy (6). Up to 30% of patients developing epilepsy will eventually be classified as having chronic epilepsy (7).

The commonest method of case ascertainment is a retrospective review of medical notes, for seizures, antiepileptic drugs, EEG or a diagnostic coding (8).

Congenital, developmental, and genetic conditions are associated with epilepsy in childhood, adolescence, and in young adults. In elderly people cerebrovascular disease is common. Head trauma, sporadic CNS infection, and tumors may occur

at any age although tumors are more likely over the age of 40. Few study found in addition that had injury, developmental delay, and a family history of epilepsy were significant risk factors.

Further investigations (EEG/CT-MRI as appropriate) should be done in evaluation of a suspected epileptic seizure (defined on basis of a careful history) to aid diagnosis, classification and prognosis (9).

Electroencephalography (EEG) is often helpful in the diagnosis and classification of epilepsy. Nonspecific EEG abnormalities are relatively common, especially in the elderly, patients with migraine, psychotic illness and psychotropic medication. Non-specific abnormalities should not be interpreted as supporting a diagnosis of epilepsy (10).

Magnetic Resonance Imaging (MRI) scanning is the current standard of reference in the investigation of patients with epilepsy. Routine MRI brain scanning using simple standard sequences will detect lesions (e.g. Small tumors, vascular malformations) that are not detected by computed tomography (CT) (11).

CT scanning has a role in the urgent assessment of seizures, or when MRI is contraindicated (e.g. when patients have pacemakers or metallic implants) (12).

This paper provides an estimation of the prevalence of epilepsy in the population in Kosovo and prevalence of side effects from the different antiepileptic drugs used for the treatment. Objectives of study are: 1. Prevalence of epilepsy (vs type of epilepsy, gender and age); 2.Types of Treatment (monotherapy/polytherapy) vs types of epilepsy, and 3. Side effects of antiepileptic drugs (carbamazepine) in patients with different types of epilepsy.

2. METHODS

In this study specialistic reports, and the histories of 294 of patients with epilepsy that have been treated with antiepileptic drugs have been analyzed and evaluated.

In my study were involved 91 (30,95%) from these patients, with identified side effects during the treatment with antiepileptic drugs: carbamazepine, ac.valproic and phenobarbitone.

For this study I have analyzed these parameters: age, gender, the history of illness, life anamnesis, electroencephalogram results, side effects of the drugs, duration of seizures, and frequency of seizures.

This study is based in pharmaco-epidemiology analyzes, retrospective-prospective study, by using the comparative method of side effects of carbamazepine, ac.valproic and phenobarbitone during the treatment of epilepsy (Primary Generalized Epilepsy, Secondary Generalized Epilepsy, Partial Epilepsy) in Neurology Clinic in University Clinical Center of Kosova (UCCK).

The pharmaceutical form of the AED (used by the patients) in this study is tablet.

Based on the diagnose of epilepsy, in study are included:

- 37 patients with Primary Generalized Epilepsy,
- 12 patients with Partial Epilepsy,
- 46 patients with Second Generalized Epilepsy,
- EEG has been done to all of 294 patients.

Statistical processing

Data presentation is done through tables and graphs.

From statistical parameters were calculated structure index, the arithmetic average, standard deviation and minimum and maximum values.

It is used the One Way ANOVA Test which is a compilation of statistical models and their common procedures, in which the observed changes, in particular variables broken down into components of different sources of this variation.

ANOVA is a statistical test used to compare many groups, and it replaces t-test. ANOVA is used when more than two groups have to be evaluated. The use of t-test for this purpose would lead to potential errors, which are avoided when ANOVA as statistical method is used.

Questionnaire composed of six units contained the following information (variables), which were studied and were statistically evaluated. These six units are:

- General information: name, surname, age, gender, birthplace, residence, diagnosis,
- Etiology (causes) of epilepsy: what the patients suspected the cause of epilepsy was: high fever, hereditary, CNS infections or trauma,
- Diagnose, what type of epilepsy the patients have: Primary Generalized Epilepsy, Partial Epilepsy, or Secondary Generalized Epilepsy,
- Therapy, is it monotherapy or polytherapy with drugs: carbamazepine, ac.valproic, phenobarbitone,
- Side effects of antiepileptic drug (carbamazepine, ac.valproic, phenobarbitone).

3. RESULTS

In the study 91 patients with epilepsy were involved from which 53 or 58.2% were female and 38 or 41.8% were male with no great significant difference between two genders (X^2=2.47, P=0.116).

Distribution of patients according to the age and types of epilepsy resulted with statistically high significant difference (F-test= 10.58, P=0.0001) between average age according to types of epilepsy.

Lower average age of patients with Primary General Epilepsy was 16.9 years (SD ± 7.4 years), and the range of 8-36 years,

Age	Gender				Total	
	Female		Male			
	N	%	N	%	N	%
1-5 year	5	9.4	2	5.3	7	7.7
6-15 year	16	30.2	14	36.8	30	33.0
16-20 year	9	17.0	8	21.1	17	18.7
21-40 year	16	30.2	6	15.8	22	24.2
41-60 year	7	13.2	4	10.5	11	12.1
>60 year	-	-	4	10.5	4	4.4
Total N	53	100.0	38	100.0	91	100.0
%	58.2	-	41.8	-	100.0	-

Table 1. Prevalence of epilepsy vs gender and age

Parameters	Gender		Total
	Female	Male	
N	53	38	91
Mean	22.1	24.6	23.2
SD	14.2	19.2	16.4
Min	2	1	1
Max	55	66	66
T-test	T=0.72		
P-value	P=0.473		

Table 2. Age vs gender parameters

followed by Secondary Generilazed Epilepsy: 24.0 years (SD ± 18.3 years), with range of 1-66 years, wile highest average age of the patients was with Partial Epilepsy: 39.5 years (SD ±18.5 years), with range of 17-65 years (Table 3).

Type of epilepsy	Treatment type				Total	
	Monotherapy		Polytherapy			
	N	%	N	%	N	%
Prim Gen Ep	34	47.2	3	15.8	37	40.7
Partial Ep	10	13.9	2	10.5	12	13.2
Sec Gen Ep	28	38.9	14	73.7	42	46.2
Total N	72	100.0	19	100.0	91	100.0
%	79.1	-	20.9	-	100.0	-

Table 4. Treatment vs type of epilepsy

Analysis of the treatment according to the type of epilepsy, nearly two thirds: 72 or 79.1% of the patients were treated with monotherapy wile 19 or 20.9% of the patients were treated with polytherapy.

According to the epilepsy types, nearly half of the patients treated with monotherapy: 34 or 47.2% were with Primary Generalized Epilepsy, followed with 28 or 38.9% with Secondary Generalized Epilepsy and only 10 or 13.9% were with Partial Epilepsy.

In 19 patients treated with polytherapy, most of them: 14 or 73,3% were with Secondary Generalized Epilepsy, followed by Primary Generalized Epilepsy with 3 patients or 15.8% and 2 patients or 10.5% with Partial Epilepsy (Table 4).

Type of epilepsy	Gender				Total	
	Female		Male			
	N	%	N	%	N	%
Prim Gen Ep	23	43.4	14	36.8	37	40.7
Partial Ep	8	15.1	4	10.5	12	13.2
Sec Gen Ep	22	41.5	20	52.6	42	46.2
Total N	53	100.0	38	100.0	91	100.0
%	58.2	-	41.8	-	100.0	-

Table 5. Types of epilepsy vs gender

Analysis of types of epilepsy according to the age group is analyzed in 53 patients or 58.2% female and 38 patients or 41.8% male patients. The lowest number of patients resulted with Partial Epilepsy with 12 or 13.2%, followed by Primary Generalized Epilepsy with 37 patients or 40.7% and most of the patients were with Secondary Generalized Epilepsy with 42 patients or 46.2%. The lowest number of cases within female group are with Partial Epilepsy resulting in 8 patients or 15.1%, and Primary Generalized Epilepsy and Secondary Generalized Epilepsy were 23 cases 43.4% and Sec Gen Ep with 22 cases 41.5% respectively. In the male group of patients there is also a similar result as in the female group: lowest number is with Partial Epilepsy with 4 cases or 10.5%, followed by Primary Generalized Epilepsy with 14 cases or 36.8% and most of the patients were with Secondary Generalized Epilepsy with 20 patients or 52.6%. (Table 5).

Secondary Epilepsy Group is present in all age groups. The highest number of cases with secondary generalized epilepsy was present in the age groups 6-15 years and 21-40 years with 11 cases each or 26.2%, in age groups 1-5 years and 41-60 years with 7 cases each or 16.7%, the incidence below 10% resulted in group ages 16-20 years with 4 patients or 9.5% and >60 years with 2 cases or 4.8% .

Age	Type of Epilesy						Total	
	Prim Gen Ep		Partial Ep		Sec Gen Ep			
	N	%	N	%			N	%
1-5 year	-	-	-	-	7	16.7	7	7.7
6-15 year	19	51.4	-	-	11	26.2	30	33.0
16-20 year	10	27.0	3	25.0	4	9.5	17	18.7
21-40 year	8	21.6	3	25.0	11	26.2	22	24.2
41-60 year	-	-	4	33.3	7	16.7	11	12.1
>60 year	-	-	2	16.7	2	4.8	4	4.4
Total N	37	100.0	12	100.0	42	100.0	91	100.0
%	40.7	-	13.2	-	46.2	-	100.0	-

Table 6. Type of epilepsy vs ages

Analysis of distribution of epilepsy cases within the age groups resulted with no Primary Generalized Epilepsy in the age group 1-5 years and over 41 years old, and more than half of the patients with this type of epilepsy were within the age group 6-15 years with 19 cases or 51.4%. Other age groups were represented with 10 cases or 27.0% in the age group of 16-20 years and with 8 cases or 21.6% in the age group of 21-40 years.

The Partial epilepsy type was not present up to the age of 15 Age groups 16-20 years and 21-40 years resulted in 3 patients in each group, or 25.0%. 4 cases or 33.3% were in the age group 41-60 years, and the lowest number of cases resulted in patients older than 60 years with only 2 patients or 16.7%. (Table 6).

The patients were treated in 64 cases or 70.3% with Carbamazepine, in 19 cases or 20.9% with Valproic acid and in 8 cases or 8.8% with Phenobarbitone. Carbamazepine 28 patients or 43.8% were with Secondary Generalized Epilepsy, 25 patients or 39.1% with Primary Generalized Epilepsy and 11 patients or 17.2% with Partial Epilepsy.(Table 7).

Type of epilepsy	Antiepileptic drug						Total	
	Carbamazepine		Ac. Valproic		Phenobarbiton			
	N	%	N	%	N	%	N	%
Prim Gen Ep	25	39.1	8	42.1	4	50.0	37	40.7
Partial Ep	11	17.2	-	-	1	12.5	12	13.2
Sec Gen Ep	28	43.8	11	57.9	3	37.5	42	46.2
Total N	64	100.0	19	100.0	8	100.0	91	100.0
%	70.3	-	20.9	-	8.8	-	100.0	-

Table 7. Treatment vs disease

Types of epilepsy were analyzed also according to the cause. Almost half of the causes were Trauma with 43 cases or 47.3%, high fever in 28 cases or 30.8%, Central nervous system infections in 12 cases or 13.2% and hereditary causes resulted in lowest number of the cases with 8 patients or 8.8%.

In the patient group with Trauma as a cause we had 22 cases or 51.2% with primary generalized epilepsy, 17 cases or 39.5% with secondary generalized epilepsy and 4 cases or 9.3% with partial epilepsy. In the patient group with high fever as a cause

Type of epilepsy	Causes								Total	
	High fever		Hereditary		CNS infections		Trauma			
	N	%	N	%	N	%	N	%	N	%
Prim Gen Ep	11	39.3	4	50.0	-	-	22	51.2	37	40.7
Partial Ep	2	7.1	-	-	6	50.0	4	9.3	12	13.2
Sec Gen Ep	15	53.6	4	50.0	6	50.0	17	39.5	42	46.2
Total N	28	100.0	8	100.0	12	100.0	43	100.0	91	100.0
%	30.8	-	8.8	-	13.2	-	47.3	-	100.0	-

Table 8. Type of epilepsy vs cause

Side effects	Antiepileptic drug						Total		Kruskal Wallis testi
	Carbamazepine		Ac. Valproic		Phenobarbiton				
	N	%	N	%	N	%	N	%	
TOTAL	64	100.0	19	100.0	8	100.0	91	100.0	
Nausea	17	26.6	1	5.3	1	12.5	19	20.9	
Drowsiness	17	26.6	5	26.3	1	12.5	23	25.3	
Dizzines	20	31.3	3	15.8	-	-	23	25.3	
Tiredenes	6	9.4	6	31.6	2	25.0	14	15.4	KW=10.50 P=0.0052
Vomiting	-	-	4	21.1	3	37.5	7	7.7	
Troub sleep	5	7.8	1	5.3	2	25.0	8	8.8	
Tremor	3	4.7	-	-	-	-	3	3.3	
Weight gain	11	17.2	3	15.8	-	-	14	15.4	
Skin rash	4	6.3	2	10.5	2	25.0	8	8.8	

Table 9. Side effects vs treatment

Side effects Carbamazepine	Type of epilepsy					
	Prim Gen Ep		Partial Ep		Sec Gen Ep	
	N	%	N	%	N	%
TOTAL	25	100.0	11	100.0	28	100.0
Nausea	8	32.0	-	-	9	32.1
Drowsiness	9	36.0	5	45.5	3	10.7
Dizziness	9	36.0	3	27.3	8	28.6
Tiredness	-	-	3	27.3	3	10.7
Vomiting	-	-	-	-	-	-
Troub sleep	1	4.0	1	9.1	3	10.7
Tremor	2	8.0	-	-	1	3.6
Weight gain	2	8.0	4	36.4	5	17.9
Skin rash	1	4.0	-	-	3	10.7

Table 10. Side effects of Carbamazepine vs type of epilepsy

there were: 15 cases or 53.6% with Secondary Generalized Epilepsy, 11 patients or 39.3% with primary generalized epilepsy, and 2 patients or 7.1% with partal epilepsy. In the group with Central Nervous System Infection as a cause there were 6 patients or 50% with Partial Epilepsy and 6 or 50% with Secondary Generalized Epilepsy, and in the group of Hereditary causes there were 4 patients or 50% with Primary Generalized Epilepsy and also 4 patients or 50% with Secondary Generalized Epilepsy (Table 8).

In patients involved in the study regardless of the type of treatment the most common side effects reported were Drowsiness and Dizziness with 23 cases or 25.3% of all patients (n=91), Nausea with 19 cases or 20.9%, Tiredness and Weight gain with 14 cases or 15.4%, Skin rash and Trouble sleeping with 8 cases or 8.8% and Tremor with 3 cases or 3.3%.

The distribution of side effects according to the antiepileptic treatment resulted in difference with high statistical significance. (KW=10.50, *P*=0.0052).

Most common side effects of Carbamazepine in all types of epilepsy were : Dizziness with 20 cases or 31.3%, Nausea and Drowsiness with 17 cases or 26.6% each , Weight gain with 11 cases or 17.2%, Tiredness with 6 cases or 9.4%, Trouble sleeping with 5 cases or 7.8%, Skin rash with 4 cases or 6.3% and Tremor with 3 cases or 4.7%. In our study, in the patients treated with Carbamazepine, no side effect of vomiting was reported.

Analysis of side effects of Carbamazepine in types of epilepsy showed that vomiting was not reported in any of the types of epilepsy, in Primary Generalized Epilepsy Tiredness was not reported and at Partial epilepsy nausea, tremor nor skin rash were not reported as side effects.

Most common side effects of Carbamazepine in Primary Generalized Epilepsy were drowsiness and dizziness with 9 cases or 36.0% each, nausea with 8 cases or 32.0%, tremor and weight gain with 2 cases or 8.0% each and trouble sleeping and skin rash with 1 case or 4.0% each. Most common side effects of Carbamazepine in partial epilepsy were drowsiness with 5 cases or 45.5%, weight gain with 4 cases or 36.4%, tiredness and dizziness with 3 cases or 27.3% and 1 case or 9.1% with trouble sleeping. Most common side effects of Carbamazepine in Secondary Generalized Epilepsy were: nausea 9 cases or 32.1%, dizziness with 8 cases or 28.6%, weight gain with 5 cases or 17.9%, drowsiness, trouble sleeping, tiredness and skin rash with 3 cases or 10.7% each, and tremor 1 case or 3.6%.

4. DISCUSSION

To ensure a maximal effectivity of the treatment and minimal side effects, a coordination between the treatment, patient and doctor should be established.

Currently in market there are many new antiepileptic drugs, but still as first line antiepileptic treatment remain carbamazepine, valproic acid and phenobarbitone. This doesn't mean that other antiepileptic drugs, especially Lamotrigine, is not in use, but this is more as a second line treatment.

According to the study results female patients had greater prevalence of epilepsy than man. The highest prevalence of epilepsy was in the group age 6-15 years old: 33.0%.

The average age of female patients was 22.1 years compared with male patients was 24.6 years, so with the t-test the average difference is not considered significant.

The average age of disease vs types of epilepsy has resulted in significant difference, with the highest average age (39.5) in Partial Epilepsy, and with the lowest in Primary Generalized Epilepsy (16.9).

With the classification of the patients by age group and gender, the difference is significant. In patients aged 21-40 years the prevalence of women vs. men is higher (30.2% vs. 15.8%), whereas in the patients aged 6-15 years the prevalence is higher among males. (F 30.2% vs. M 36.8%).

The prevalence of epilepsy was higher in females 30.2% (in age group 21-40 years) compared with men 15.8%, and this may be due to the increased exposure of adult female toward trauma during the war in our country, due to socioeconomic factors, our mentality, and also predisposition of females against epilepsy.

In patients over 60 year old the number of men affected by epilepsy in our study is higher, as a result of possible infections in CNS, tumors, without ignoring the influence of the hazardous working environment. In our country, males are predominantly engaged in working places with hazardous and stressful environment.

About 50 million people worldwide have epilepsy, with most 90% of these people being in developing countries(13). Epilepsy is more likely to occur in young children or people over the age of 65 year; however it can occur at any time. As consequence of brain surgery epileptic seizures may occur in recovering patients. Epilepsy is usually controlled, but cannot be cured with medication, although surgery may be considered in difficult cases. However 30% of people with epilepsy do not have seizure control even with the best available medications. Not all epilepsy syndromes are lifelong, some forms are confined to particular stages of childhood. Epilepsy should not understand

as a single disorder, but rather as syndromes with vastly divergent symptoms but all involving episodic abnormal electrical activity in the brain (14).

From hospital and clinic studies it is well known that the range of etiologies in the epilepsies varies in different age groups and also according to geographic location. Approximately 75% of all cases of epilepsy have no known causes. This is referred to as idiopathic epilepsy. The other 25% of cases have known the etiology (15). In the United Kingdom National General Practitioners study of epilepsy, seizures were classified as idiopathic in 72%, remote symptomatic in 25%, and the remaining 3% were associated with neurological deficits present at birth (16).

Most reports show slightly higher rates in males than in females. This is because the females consult their general practitioner for episodes of disturbed consciousness of any sort twice as often as males (17). There are also several small scale reports showing high rates in black population. A lower standard of perinatal care might be relevant and socioeconomic factor (5).

Incidental epileptiform abnormalities are found in 0.5% of healthy young adults, but are more likely in people with learning disability and psychiatric disorders, patients with previous neurological insult (e.g. meningitis, stroke, cerebral palsy) and patients who have undergone neurosurgery (18). The finding of epileptiform abnormalities is specific and the diagnostic value of the test is good. In a patient in whom the history is typical of some other disorder, the prevalence of epilepsy will be low, and any epileptiform abnormalities are more likely to be incidental, the test should not be performed in this circumstances (19).

It is worth mentioning that as accurate as diagnosis can be the possibility of the appearance of side effects is less possible.

5. CONCLUSION

- Based on the analysis of results of the study, literature review and publications I may consider that:
- Unwanted side effects of antiepileptic drugs analyzed in the study are frequent, but not so severe as to be life threatening. Treatment of epilepsy with these three drugs (carbamazepine) would be the first choice of treatment, with the best safety and efficacy. Application of this therapy is rarely compromised because of the appearance of unwanted side effects. Replacement or termination of therapy may be applied if actual therapy is not adequate for the management of epileptic attacks.
- In general, therapy with these three antiepileptic drugs is well tolerated by the organism, and most patients feel better as a result of this therapy, which was evidenced by the results of good management of epileptic attacks in our study patients.
- The greatest number of patients reported Trauma as the cause of epilepsy with 43 cases or 47.3%. Hereditary causes resulted in lowest number of the cases with 8 patients or 8.8%.
- Epilepsy should be treated continuously, by carefully choosing appropriate therapy. In particular, it is important to ensure a proper approach in management of epilepsy always considering life quality and life length of the patients.
- As we know the epilepsy cannot be cured, but it can be managed with a careful choice of an effective treatment and dosage.
- We hereby declare: that the manuscript is original and the work has not been published elsewhere.

CONFLICT OF INTEREST: NONE DECLARED.

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