Assessment of Haematological Parameters in Patients under Carbamazepine Antiepileptic Drug Treatment

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ABSTRACT

AIM Carbamazepine is iminostilbene derivative used as an antiepileptic drug against partial and tonic-clonic seizures and is also used in trigeminal neurologic and bipolar affective disorders. According to previous studies, carbamazepine is associated with a wide range of haematological toxicities including leucopenia, reduced haemoglobin and red blood cell count, and thrombocytopenia.
This study was conducted to establish the effect of carbamazepine as an antiepileptic drug in haematological parameters in patients using it for different durations.

METHOD In this study, 50 individuals were recruited as the study group and 50 individuals as the control group. Seventeen patients were female while 33 were male in the study group. Twenty-two were female and 28 were male in the control group. In both groups age-range was 15-70 years. We included patients under treatment for at least one month. Subjects with neurological deficits, haematological deficits, or history of drugs/ alcohol abuse at recruitment were excluded from the study. Route of administration was oral. Blood samples (2.5 ml each sample) were collected from all patients and controls in Ethyelene diamine tetra acetic acid (EDTA) blood tubes, Full Blood Counts (FBCs) were carried out using automated Huma count 30 cell counter.

RESULTS In this study administration of carbamazepine at different doses, different duration and with different severity of disease produced slight differences in mean haemoglobin, haematocrit and white blood cell count with p value > 0.05. The mean platelet counts were also within normal range in all patients. Addition of folic acid to carbamazepine therapy did not produce any clinically significant changes in haematological parameters. Our study did not reveal any significant relationship between severity of disease, duration or dose of carbamazepine and changes on FBC results.

CONCLUSION Carbamazepine had no significant difference in FBC parameters among epileptic patients who used it as treatment.

Keywords: Blood Cell Count; Carbamazepine; Antiepileptic Drug; Epilepsy; Anaemia; Leukopenia; Thrombocytopenia.

INTRODUCTION

Epilepsy is a chronic condition characterized by repeated and intermittent seizures caused by abnormal electrical activity within the brain, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of awareness. [1] Epilepsy is the second most chronic neurological condition seen by

neurologists. The incidence of epilepsy ranges from 40 to 70 per 100,000 in most developed countries and from 100 to 190 per 100,000 in developing countries. [2] Epilepsy seizures may be tied to genetic factors [3-4] or brain injury, but in 70 percent of epilepsy patients the cause is unknown. [5]

Antiepileptic drugs (AED) cannot stop the mechanisms that cause epilepsy but they can reduce the recurrence of seizures or completely stop the seizures without causing general depression in central nervous systems during usage. [6] Carbamazepine is aiminostilbene derivative used as an antiepileptic drug against partial and tonic-clonic seizures as well as in trigeminal neurologic and bipolar affective disorder. [7] It is a white to off-white powder [8] with a melting point of 190.2 degrees Celsius, [9] soluble in alcohol, Acetone, propylene glycol; and practically insoluble in water. [10] The mechanism of action of carbamazepine is by stabilizing the inactivated state of voltage gated sodium channels, making fewer of these channels available to subsequently open. This leaves the affected cells less excitable until the drug dissociates. Carbamazepine has also been shown to potentiate GABA receptors made up of alpha-1, beta-2 and gamma-2 subunits. [11] About 75% of carbamazepine in plasma is protein bound. [12] It is metabolised extensively by hepatic mixed-function oxidase system, yielding primarily the 10, 11- epoxide which is quite stable, pharmacologically active and found in plasma and tissue. The 10, 11-epoxide is then metabolised further to 10, 11-dihydroxide and eliminated in the urine as such and also as conjugates of glucuronic acid. [13]

According to previous studies carbamazepine is associated with a wide range of haematological toxicities including leucopenia, [14] anaemia, agranulocytosis [15-16] and thrombocytopenia. [17] Numerous studies have examined and found that carbamazepine induces oxidative stress via formation of free radical oxygen species (ROS). ROS are produced from oxidative metabolism and inhibit all antioxidant enzyme activities, reduce glutathione content [18] and enhance damage on cellular macromolecules, finally leading to cell death. [19] Folate deficiency may result from accelerated metabolism of folate due to induction of liver enzymes by carbamazepine causing macrocytosis of red blood cells and leucopenia. [20-21] Carbamazepine has also been reported to produce prominent bone marrow suppression leading to haematological toxicity. [22]

This study was conducted to establish the effect of carbamazepine as an antiepileptic drug in haematological parameters and its relation to the duration of treatment.

METHODS

This case control study was conducted in Khartoum state at Altegani Almahi Hospital for neurology and psychiatry in 2015. A total of 50 individuals diagnosed with epilepsy and receiving carbamazepine monotherapy treatment and 50 normal individuals as control group were recruited in this study. The study was done in both male and female patients aged 15-70 years. Subjects with neurological and haematological deficits, history of drugs/alcohol abuse were excluded from the study. Route of administration of carbamazepine was oral.

SAMPLES Blood samples (each 2.5 ml) were collected from all patients and controls in EthyeleneDiamine Tetra acetic acid (EDTA) blood tubes. Full blood count (FBC) were carried out using automated Humacount 30 cell counter.

STATISTICAL ANALYSIS Data were processed using Microsoft Excel and statistical package for social sciences (SPSS, version18) for windows. The variables of interest were severity of the disease, dose and duration of carbamazepine, and coadminstration of carbamazepine and folic acid and FBC parameters. The mean of variables was determined and then studied for significance using the p-value.

ETHICAL CONSIDERATION This study was approved by the ethical research committee of medical laboratory sciences, Al-Neelain university and informed consent was obtained from all participants in accordance with the requirements and guidelines of the ethical committee before sample collection.

RESULTS

The mean haemoglobin (Hb), haematocrit (HCT) and red blood cell counts (RBCs) in the study group were 13.7 g/dl, 40.5% and 4.9 x 10^6/mm^3 respectively with a p-value of >0.05 when compared to the mean Hb, HCT, RBCs in the control group which were 13.6 g/dl, 40.5%, and 4.9 x 10^6/mm^3 respectively. The mean total white blood cell count (WBC), absolute neutrophil count, lymphocyte count in the study group were 5.6 x 10^3/mm^3, 2.2 x 10^3/mm^3, and 2.2 x 10^3/mm^3 respectively with a p-value of >0.05 as compared to those of the control group which were 5.6 x 10^3/mm^3, 3.0 x 10^3/mm^3, 2.6 x 10^3/mm^3 respectively. The mean platelet count was 249 x 10^3/mm^3 in the study group with a p-value of 0.06 by comparison with that of the control group (276 x 10^3/mm^3), (Table 1).

Table 1. Haematological parameters of patients and controls.

Parameter	Patient (mean)	Control (mean)	P.Value
Hb (g/dl)	13.68	13.58	0.717
HCT (%)	40.47	40.54	0.935
RBC (x10^6/mm^3)	4.90	4.87	0.783
WBC (x10^3/mm^3)	5.58	5.60	0.782
Absolute neutrophil count (x10^3/mm^3)	2.17	3.03	0.191
Absolute lymphocyte count (x10^3/mm^3)	2.17	2.0	0.199
Platelet count (x10^3/mm^3)	249.6	276.6	0.060

P.value >.05 means no significant difference.

The frequencies of mild, moderate and severe disease among the study group were 24 patients (48%), 23(46%) and 3(6%) respectively. No statistical correlation (p.value >.05) was found between the severity of disease and the results of FBC parameters (Table 2).

Table 2. Mean haematological parameters at different levels of disease severity.

Parameters	Mild	Moderate	Severe	P-value
Hb (g/dl)	13.5	13.8	13.4	>.05
Hct (%)	39.9	41	39.8	>.05
RBC (x10^6/mm^3)	4.7	4.9	4.7	>.05
Platelet (x10^3/mm^3)	240	259	251	>.05

Mean platelet counts for different treatment durations (<1year, 1-10years, >10years) were 207 x 10^3/mm^3, 267 x 10^3/mm^3 and 235 x 10^3/mm^3 respectively. None of the patients had thrombocytopenia (Table 3).

Table 3. Mean haematological parameters at different treatment durations.

Parameters	<1 year	1-10 years	>10 years	p-value
Hb (g/dl)	14.2	13.6	13.6	>.05
Hct (%)	42.3	40.3	40.2	>.05
RBC (x10^6/mm^3)	5.2	4.8	4.8	>.05
Platelet (x10^3/mm^3)	207	267	235	.025

Carbamazepine doses were 200-400 mg (24 patients, 48%), 600-800mg (23 patients, 46%), and >800mg (3 patients, 6%). These showed no statistical correlation (p.value>.05) with FBC parameters (Table 4).

There were no clinically significant changes in haematological parameters with the addition of folic acid to carbamazepine. Mean Hb (13.9g/dl), HCT(41.1%) and WBC (5.7 x 10^3/mm^3) in patients taking carbamazepine with 5mg folic acid produced no significant difference with (p.value>0.05) as compared to mean of Hb (13.3g/dl), HCT (38%) and WBC (6.3 x 10^3/mm^3) in patients taking carbamazepine alone.(Table 5).

Table 4. Mean haematological parameters at different doses of carbamazepine.

Parameters	200-400 mg	600-800 mg	>800 mg	P-value
Hb (g/dl)	13.5	13.8	13.4	>.05
Hct (%)	39.9	41	39.8	>.05
RBC (x10^6/mm^3)	4.7	4.9	4.7	>.05
Platelet (10^3/mm^3)	240	259	251	>.05

Table 5. Mean haematological parameters in patients taking carbamazepine with and without folic acid

Parameter	CBZ & folic acid	CBZ alone	P-value
Hb (g/dl)	13.9	13.3	>.05
HCT (%)	41.1	38	>.05
RBC (x10^6/mm^3)	4.84	4.85	0.01
Platelet (x10^3/mm^3)	238	263	0.025-0.01

DISCUSSION

Numerous studies have found that carbamazepine is associated with a wide range of haematological toxicities. Our study showed minor differences in mean white blood cell count, mean red blood cell count and mean haemoglobin level between different degrees of disease severity, between different doses of carbamazepine, and different treatment durations. Although these differences were not statistically significant in our study, the fact that they were not clinically significant is in general agreement with the findings of Jarvi et al [23] which showed that there were mild changes in these haematologic parameters during carbamazepine therapy, with the mean WBC of 7.5 x 10^3/mm^3 at diagnosis and a decrease after 2 months (to 5.8 x 10^3/mm^3) of carbamazepine treatment. This remained at this lower level during first 5 years of treatment (5.6 x 10^3/mm^3 p-value<0.001). Furthermore, a slight decrease was found in the mean red blood cell count after 2 months of carbamazepine treatment (from 4.7 x 10^6/mm^3 to 4.5 x 10^6/mm^3, p-value <0.001). Mean haemoglobin level dropped to 13.8g/dl from 14.2g/dl during the first 12 months of carbamazepine treatment and returned to normal during first 5years of medication.

The pathophysiological mechanism of carbamazepine-induced thrombocytopenia has not been firmly established, and further studies are required. [24] An immune mechanism has been proposed, with an antibody-mediated destruction of platelets in peripheral blood in the absence of bone marrow suppression. [25] Anti-IgG carbamazepine-dependent platelet reactive antibodies have been identified in blood. [26] In the present study, however, mean platelet count with different duration of carbamazepine use <1year, 1-10years, >10years were 207 x 10^3/mm^3, 267 x 10^3/mm^3, 235 x 10^3/mm^3 respectively. The platelet counts were within normal limits in the three groups. However, the mean platelet count showed an increase between <1 year and 1-10 years then dropped between 1-10 years and >10 years. The effect of carbamazepine on platelets appears to be a combination of reactive thrombocytosis and peripheral destruction of the platelets. [27] The underlying platelet count may be a balance of these two processes with perhaps the majority of cases having increased platelet count while a few patients develop thrombocytopaenia. Crespo et al found that four patients (2 males and 2 females) treated with carbamazepine (2.9% of the study population) had thrombocytopenia with platelet count range of 112-148 x 10^3/mm^3. [27] Demonstration of clinically significant combination of thrombocytosis and peripheral destruction of platelets as an effect of carbamazepine therapy may require greater number of patients.

Carbamazepine reduces serum folate [28] and it is suggested that haematological parameters may be affected by carbamazepine therapy owing to changes in folate metabolism [23] It was suggested that folate deficiency may result from accelerated metabolism of folate owing to induction of liver enzymes by anticonvulsant drugs. [29] In the present study, there were no clinically significant differences in the mean values of haematological parameters among patients taking carbamazepine with 5mg folic acid as compared to patients taking carbamazepine alone.

CONCLUSION

The usefulness in clinical practice of full blood count monitoring at initiation, and during carbamazepine treatment is a controversial issue. Our study found no significant difference in FBC parameters among epileptic patients who used carbamazepine as treatment.

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