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Incidence of Anaemia in Epileptic Patients Using Carbamazepine or Phenytoin. A Retrospective Cohort Study

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Abstract

Background: Carbamazepine and phenytoin are the mainstays of epilepsy treatment. The antiepileptics depend on the patient's condition and ensure seizure control without causing any adverse effects, such as anaemia. Anaemia is not a life-threatening condition; however, it disrupts the outcomes of epilepsy patients.

Purpose: The main purpose of the study was to investigate and associate the use of carbamazepine and phenytoin in adult epilepsy patients and the anaemia incidence.

Materials and Methods: A retrospective cohort study was performed between January 2020 and February 2023 at King Saud University Medical City. The study involved adult patients with epilepsy treated with carbamazepine or phenytoin independently or in addition to the Antiepileptic drug regimen. Patients 18 years or older were eligible for the study. Patients with a history of anaemia before starting carbamazepine or phenytoin, or any comorbidities besides epilepsy, were excluded as they can disrupt blood measurements. The primary outcome was the incidence of anaemia as per WHO criteria. The secondary outcomes highlighted the incidence of anaemia and types of epilepsy, folic acid supplements, and the drug serum level. The study employed the Shapiro Wilk test to measure data normality, the Mann–Whitney U test to link non-normally distributed variables, Pearson's Chi-square and Fisher's Exact tests to examine categorical variables, and Pearson's correlation test. A significance level set at $p < 0.05$.

Results: A total of 724 participants, aged 37 (27-48) years, were treated with carbamazepine, whereas 300 participants, aged 46 (33-55) years, were treated with phenytoin. The results of multivariable logistic regression analyses aligned with the univariate analyses regarding female subjects treated with carbamazepine. The females treated with carbamazepine had 2.33 times (95% CI: 1.39-3.87) ($p = 0.001$) was possible to have anaemia than those treated with phenytoin. A significant correlation was found between phenytoin plasma concentration and the incidence of anaemia in female subjects ($p = 0.002$). The most common type of anaemia based on Mean Corpuscular Volume was normocytic anaemia, and the highest occurrence of anaemia was mild to moderate in both groups.

Conclusion: The most common antiepileptic drugs are carbamazepine and phenytoin; however, they pose some side effects, including anaemia, particularly normocytic anaemia. The study is beneficial in the healthcare system, highlighting the importance of drug therapy in patients with epilepsy.

Keywords: Carbamazepine, phenytoin, anaemia, epilepsy, seizures.

Introduction

Epilepsy is one of the typical chronic neurological illnesses. The condition can affect any age group and is characterized by epileptic seizure episodes [1]. The occurrence of present epilepsy is 6.38 out of 1,000 persons (95% CI 5.57-7.30) [2]. In the region of Arab, the median prevalence of active epilepsy is 4.4 out of 1,000 persons (95% CI 2.1–9.3) [3]. The current prevalence study for active epilepsy cases revealed an estimated 3.96 out of 1,000 persons (95% CI 2.99-5.16) in the Kingdom of Saudi Arabia (KSA) [4]. As per International League Against Epilepsy (ILAE), epilepsy is categorized by the existence of any of the resulting conditions: The two senseless (or reflex) seizures arising >24 hours apart, or one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years or diagnosis of an epilepsy syndrome [5].

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In 2017, the ILAE updated the seizure kinds which consist of three levels: type of seizures, epilepsy kinds, and disease pattern. Types of epilepsy include focal epilepsy, generalized epilepsy, combined (generalized and focal) epilepsy, and an unknown type. Causes include: structural, genetic, infectious, metabolic, immune, or unknown. Additionally, comorbidities should be identified at each stage [6]. The risk of comorbid diseases in epilepsy patients is prominent alongwith somatic, psychological, and behavioural disorders being more common than in the general population [7, 8].

The treatment of epilepsy commonly involves Antiepileptic drugs (AEDs), and it has been observed that 50% of patients become seizure-free following the first therapy trial [9]. Most patients can be treated with conventional AEDs such as carbamazepine, phenytoin, and valproic acid. In addition, new generation AEDs such as levetiracetam, lamotrigine, topiramate, and tiagabine are currently used as an add-on or alternative therapy [10].

Carbamazepine and phenytoin are the earliest drugs recommended for most types of seizures. Carbamazepine is more commonly prescribed in the USA and Europe; however, phenytoin is widely prescribed in lower and middle-income districts of Africa, Asia, and South America [11]. Although carbamazepine and phenytoin act particularly on voltage-gated sodium channels, they possess various pharmacokinetic and pharmacodynamic properties, affecting their safety and effectiveness [12]. Carbamazepine has an oral bioavailability of 75 to 85%, and it is approximately 75% protein-bound and 90% metabolized in the liver by CYPs 3A4 (major) and 1A2 and 2C8 (minor) to active (epoxide) and inactive metabolites. It is a potent and broad-spectrum inducer of the CYP, UGT-glucuronidation, and P-gp [13]. On the contrary, phenytoin has an oral bioavailability of 70 to 95%; with 90 to 95% protein-bound and 90% metabolized in the liver by CYPs 2C9, 2C19, 3A4 (minor) and non-CYP transformations to inactive metabolites. It is a potent and broad-spectrum inducer of CYP and UGT-glucuronidation [14].

In addition, the carbamazepine removal half-life is approximately 25 to 65 hours after the initial dose, then 8 to 22 hours after numerous weeks due to auto-induction. On the other hand, phenytoin is not a first-order drug and follows Michaelis-Menten pharmacokinetics, which indicates that half-life increases with increasing phenytoin concentration [15]. The pharmacokinetic profile is summarized in Table 1. Serum carbamazepine levels should be calculated initially at three, six, and nine weeks due to autoinduction with a goal of 4 to 12 mcg/mL (SI: 17 to 51 micromole/L). Subsequently, regularity should be checked at least every two months until successive determinations are constant, and more frequently if carbamazepine or concomitant AEDs doses are changed [16]. Plasma phenytoin concentrations are drawn within five to eight days of therapy initiation.

This study is the first study in the KSA to compare the incidence of anaemia and significant changes in the haemotology elements of the complete blood count (CBC) between patients taking carbamazepine and those taking phenytoin; however, there is not enough data consensus on which drug causes haematological side effects. Hence, this study targets two of the most widely prescribed AEDs and considers cornerstones for treating epilepsy. Several observational studies conducted outside KSA have produced a variety of findings due to genetic differences among individuals, influencing pharmacokinetics and pharmacodynamics interactions consistent with the pathogenetic mechanisms of anaemia caused by AEDs,

Table 1: Pharmacokinetic profile of carbamazepine and phenytoin

	Carbamazepine	**Phenytoin**
Oral bioavailability (%)	75 -85	70 - 95
Protein binding (%)	75	90-95
Liver metabolism	CYPs 3A4 (major) CYPs 1A2/2C8 (minor)	CYPs 2C9, 2C19, 3A4 (minor) and non-CYP
Enzyme or transporter	Inducer of CYP, UGT-glucuronidation, and P-gp	Inducer of CYP and UGT-glucuronidation
Half-life in adults (hours)	25 - 65 (naive patient) 8 – 22	Dose-dependent
Therapeutic level range	4 to 12 mcg/mL	10 to 20 mcg/L

which must be evaluated in real-world settings [17]. The pharmacokinetic profile is summarized in Table 1.

The objectives of the study included the evaluation of the frequency of anaemia induced by carbamazepine and phenytoin in adult patients with epilepsy. To investigate the impact of the dosage of carbamazepine and phenytoin on the incidence rate and severity of anaemia. Assessment of the connection between the incidence of anaemia and sociodemographic factors of carbamazepine and phenytoin users. Additionally, it will explore and compare the incidence of anaemia in different seizure types among carbamazepine and phenytoin users. Moreover, to compare the kinds of anaemia induced by phenytoin and carbamazepine.

Literature Review

Anaemia can provoke seizures through different triggers and mechanisms, such as a decrease in neurotransmitters, changes in neuron metabolism, enzyme reduction, and impairment in oxygenation and energy metabolism of the brain [18]. Furthermore, anaemia may decrease the seizure threshold and increase seizure activity [19]. However, some studies believe it may be a defensive aspect [20]. Additionally, many studies found iron deficiency anaemia associated with feverish seizures in children [21]. Moreover, epilepsy in sickle cell anaemia is more typical than in the general population [22].

Pathophysiology of Anemia by Antiepileptic drugs

Many AEDs are associated with haematological disorders with a spectrum of haematological anomalies that range from mild thrombocytopenia or neutropenia to anaemia, red cell aplasia and bone marrow failure [23]. According to the World Health Organization (WHO), anaemia affected by AEDs corresponds to type B and type C [24]. Type B effects are direct cytotoxic or immunologic reactions induced by AEDs or their metabolites, and type C effects are idiosyncratic and chronic cumulative dose effects [25]. AEDs induce different types of anaemia, including aplastic anaemia, which is related to the suppression of the bone marrow [26]. Hemolytic anaemia is both immune and immune-mediated [27]. In contrast, megaloblastic anaemia occurs due to folate deficiency associated with chronic drug use and cumulative dose effect [28]. The pathogenetic mechanisms at the basis of haematological complications caused by AEDs are still unknown and are related to an immunological mechanism; however, drug pharmacokinetics and pharmacodynamics interactions are also essesntial [27].

Association of Anemia with epilepsy and antiepileptic drugs

According to past literature, various AEDs were associated with multiple adverse effects, including haematological effects. One typical adverse effect in adult and young patients is anaemia. The study by Handoko et.al (2006) reported that carbamazepine had (Odds Ratio (OR), 10.3; 95% CI, 2.0–101), valproic acid had (OR, 18.2; 95% CI, 2.5-∞), and phenytoin had (OR,3.5; 95% CI, 0.4–44.4), overall, OR was lower, but still clearly increased (adjusted OR, 9.5; 95% CI, 3.0–39.7). They found that carbamazepine and valproic acid were significantly associated with a ninefold augmented risk of aplastic anaemia. Combination therapy with AEDs was more strongly related to aplastic anaemia than monotherapy[29].

A retrospective observational study by Pottoo et.al (2019) assessed the prescription patterns of AEDs, hematobiochemical changes, and adverse effects in the eastern province of KSA. The AEDs investigated in this study were carbamazepine, phenytoin, and valproic acid as monotherapy or combined with other AEDs. This study included 118 patients with epilepsy; 54 patients were females, while 64 were males. The number of patients treated with carbamazepine was 47, valproic acid was 32 patients, and phenytoin was 10 patients as monotherapy. The remaining patients were treated with combination therapies. The findings revealed that monotherapy had a less decreased effect on haemoglobin levels with no statistical significance. At the same time, the combination therapy had a reduced impact on haemoglobin levels with no statistical significance [30].

Additionally, an open-label randomized clinical trial by Asadi-Pooya et al (2006) was performed from January 2002 to August 2004 in epilepsy patients to assess the effect of folic acid supplements on preventing carbamazepine-induced haematological instabilities. The patients were monitored for one year, and data were analyzed with t-tests and Pearson's v2 tests to compare haematological indices at baseline and after therapy follow-up. A probability value of <0.05 was considered significant. The researchers found that haemoglobin concentration dropped in Group one but rose slightly in Group two; these changes were statistically significant. On the contrary, there were no significant differences between the two groups in platelet count, monocyte count, Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), and

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Mean Corpuscular Haemoglobin Concentration (MCHC) [31].

Another retrospective observational study was conducted to assess haematological parameters in epileptic children on AEDs. The study occurred from December 2017 to April 2018, and included 83 pediatric patients; 43 were females, while 40 were males. The researchers divided patients into three groups as per the amount of AED managements. The patient sample age ranges from one year to 17 years old. The results found that regardless of the number of AED therapies used in all the treated patients, the average haemoglobin level was significantly decreased ($P = 0.05$ was considered statistically significant), especially in the female gender. However, there are insignificant changes in other haematological parameters in both genders of patients [32].

Furthermore, a cross-sectional study to evaluate the effects of AEDs on haematological parameters among 255 adult patients (144 males and 111 females) with confirmed diagnoses of epilepsy and who received carbamazepine as monotherapy for at least one month was conducted; however, patients were excluded if they had conditions that affected haematological parameters. Nevertheless, there was no variance in the reduction in haemoglobin intensities found in females compared with males, nor was it different in all other haematological parameters [33].

Moreover, it is based on AEDs-induced hemolytic anaemia by several mechanisms, such as hapten, non-hapten immune-related hemolysis, and oxidative reactions [27]. One case reported hemolytic anaemia after five weeks of use of carbamazepine in a 5-year-old boy [34]. The other cases were after the use of phenytoin reported by [35]

The past literature has particularly focused on the management of seizures through drug therapy without assessing the haematological side effects, including anaemia. Additionally, the social, environmental and genetic factors associated with drug-associated anaemia remain unexplored. A limited amount of data has been found on the common types of drug-induced anaemia and different kinds of seizures. Furthermore, studies discussing the haematological effects of AEDs in Saudi adult populations are inadequate. The current study is to explore the association between adult epilepsy patients' utilization of carbamazepine and phenytoin and their occurrence of anaemia.

Methodology

Study Design and Setting

A single-centre, retrospective cohort study was executed from January 2020 to February 2023 at King Saud University Medical City (KSUMC), a 1000-bed tertiary care teaching hospital in Riyadh, Saudi Arabia.

Study Participants

The study included 1054 participants, divided into two groups: participants receiving carbamazepine (n=724) and participants receiving phenytoin (n=300). Additionally, a total of n=30 received carbamazepine and phenytoin together (Appendix E). Data from patients' electronic medical records (EMRs) were used to identify patients prescribed carbamazepine or phenytoin for epilepsy.

Eligibility Criteria

The following are the eligibility criteria;

Inclusion Criteria

i. Patients taking carbamazepine or phenytoin alone or in combination as part of the AEDs regimen.
ii. 18 years old or above patients
iii. Patients with serum haematological parameters of the complete blood count.

Exclusion Criteria

i. Patients with age <18 years old.
ii. Patients with a history of anaemia before starting the carbamazepine or phenytoin
iii. Patients with other comorbidities besides epilepsy that could affect blood parameters
iv. Patients with autoimmune disease, chronic kidney disease, chronic hepatitis, or inflammatory bowel disease
v. Pregnant or breastfeeding women who have had recent surgery.
vi. Patients with a history of chemotherapy and immunosuppressive drugs.

Patients with no information on serum of CBC were 277 (17.54%) out of 1579

Data collection

The data were obtained from EMRs using the Cerner Millennium system (eSIHI) used at KSUMC. The information was collected using an Excel spreadsheet (Appendix A). The patient's demographic information, age, gender, body weight, and height. The date the patient started the carbamazepine and phenytoin, with doses and frequency. The classes of epilepsy were collected according to the 2017 ILAE classification. The concurrent

medications and other medical histories were obtained. Furthermore, the following variables were being collected: serum haematological parameters including haemoglobin, hematocrit, platelet count, MCV, MCH, MCHC, white blood cell count, serum level of carbamazepine, and plasma level of phenytoin (total phenytoin levels).

Ethical consideration

The research and ethics committees at the KSUMC approved the study. Due to the nature of this study, which was non-interventional and retrospective, no consent was required from patients. Institutional Review Board (IRB) approval was obtained from KSUMC with project number E-23-7928 (Appendix B). The IRB at Riyadh Elm University, registration number FPGRP/2023/781/1024 (Appendix C).

Primary and Secondary Outcomes

The primary outcome was the universal occurrence of anaemia; according to the WHO criteria, anaemia in adults is well-defined as haemoglobin levels less than 120 g/l in women and less than 130 g/l in men. The WHO classified the severity of Anemia based on blood hemoglobin level for women as mild Anemia: 110-119 g/l, moderate Anemia: 80-109 g/l, and severe anemia: lower than 80 g/l, and for men mild Anemia: 110-129 g/l, moderate Anemia: 80-109 g/l, and severe Anemia: lower than 80 g/l [36]. Anaemia severity classifications (haemoglobin values in grams per litre) are summarized in Table 2. In contrast, the secondary outcome focused on the association between the incidence of anaemia and types of epilepsy and folic acid supplement, as well as the correlation between the incidence of anaemia and drug serum level; in addition, the kinds of anaemia based on the MCV were set on the following criteria.

In anaemic subjects, MCV less than 80 fl indicates microcytic anaemia, MCV between 80 and 100 fl indicates normocytic anaemia, and MCV greater than 100 fl indicates macrocytic anaemia [37].

Table 2. The severity of anaemia was classified according to WHO criteria (haemoglobin values in grams per litre)

Population	Mild (g/L)	Moderate (g/L)	Severe (g/L)
Non-pregnant women (15 years of age and above)	110–119	80–109	< 80
Men (15 years of age and above)	110–129	80–109	< 80

Statistical analysis

A Statistical Package for Social Sciences (SPSS) version 26 was used for statistical analysis. In descriptive statistics, non-normally distributed scale data were presented as a median, and the Interquartile Range (IQR) and categorical variables were described as frequency and percentages. Correlations between categorical variables were tested using Pearson's Chi-square/Fisher's exact test, and between scale variables by Pearson's correlation test. Means of non-normally distributed scale data were compared using the Mann-Whitney U test. A P-value less than 0.05 was considered statistically significant for all analyses. The Shapiro-Wilk test (Appendix D) checked the normal distribution for scale data.

Results

A total of 1054 participants were included in the study, as shown in Figure 1. The applicants were classified into two groups: participants receiving carbamazepine (n=724) and participants receiving phenytoin (n=300). In addition, a total of n=30 received carbamazepine and phenytoin together (Appendix E). The Median (IQR) age of the carbamazepine users was 37 (27-48), while phenytoin users were slightly older, at 46 (33-55). The Median (IQR) BMI of the carbamazepine group was 27.4 (23-31) Kg/m2, and the phenytoin group was 27.7 (25-33) Kg/m2. Most participants were male in both groups; 54.3% were in the carbamazepine group, and 59% were in the phenytoin group. The generalized epilepsy was observed in both groups, 58.7% in % carbamazepine group, and 66.8% in the phenytoin group. The epilepsy classification data were missing in 94 cases of the carbamazepine group and 35 cases of the phenytoin group. The Median (IQR) serum carbamazepine level was 8.3 (6.2-10.7) mcg/l, within the normal range of 4 to 12 mcg/ml. The Median (IQR) plasma phenytoin level was 14.6 (11.4-17.1) mcg/ml, within the normal range of 10 to 20 mcg/L using total phenytoin levels. In the carbamazepine group, 52.9% of the cases received antiepileptic monotherapy (carbamazepine alone). In contrast, 49.3% of the participants in the phenytoin group received antiepileptic monotherapy (phenytoin alone) as shown in Table 3.

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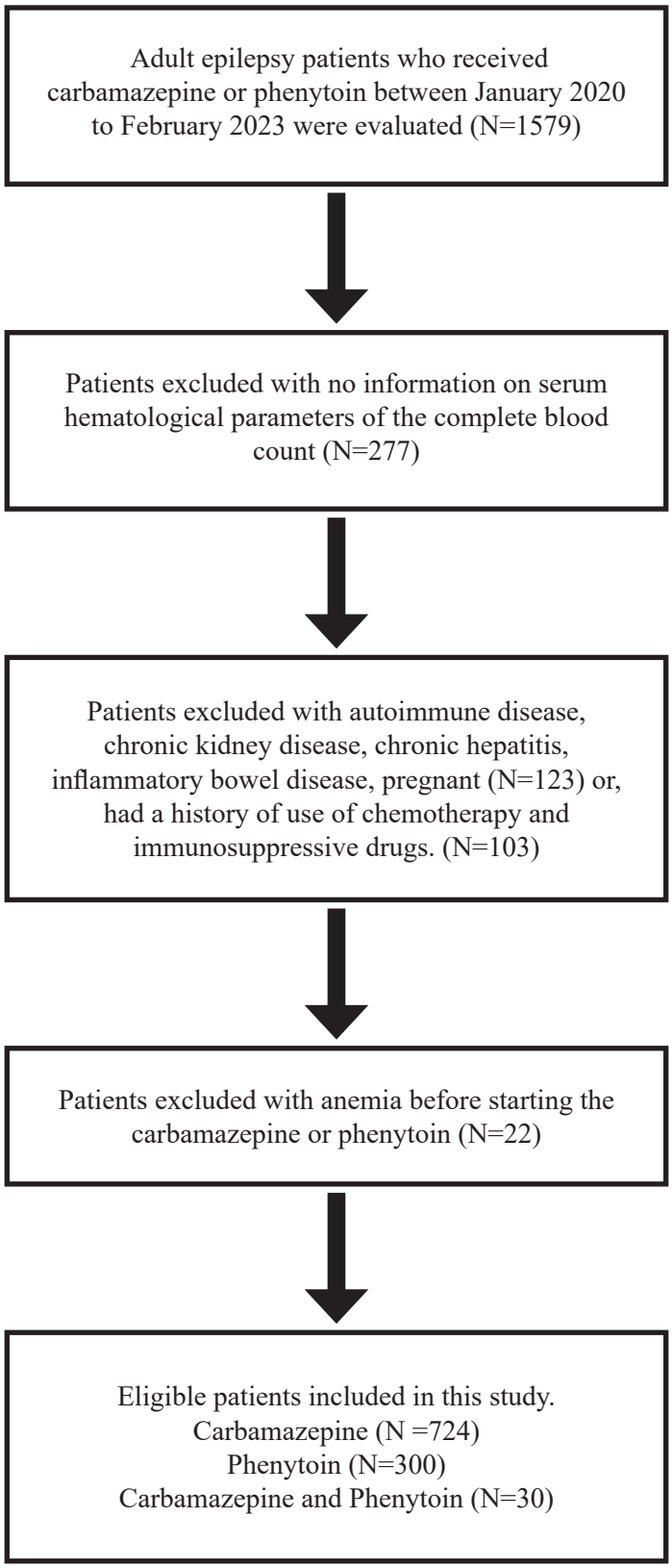

Figure 1: Patient selection criteria

Table 3: Demographic and baseline characteristics among both carbamazepine and phenytoin groups.

		Carbamazepine	Phenytoin	P Value
Number of Subjects		724	300	
Age [Years, Median (IQR)]		37 (27-48)	46 (33-55)	< 0.001M
BMI [Kg/m2, Median (IQR)]		27.4 (23-31)	27.7 (25-33)	0.576M
Weight [Kg, Median (IQR)]		74 (61-86)	75 (64-85)	0.955M
Height [cm, Median (IQR)]		164 (158-170)	162 (155-169)	0.249M
Gender [(Frequency (%)]	Male	393 (54.3%)	177 (59%)	0.167C
	Female	331 (45.7%)	123 (41%)	
Types of epilepsy [(Frequency (%)]	Focal	209 (33.2%)	67 (25.3%)	0.021C*
	Generalized	370 (58.7%)	177 (66.8%)	0.021C*
	Combined	47 (7.5%)	17 (6.4%)	0.459C
	Unknown	4 (0.6%)	4 (1.5%)	0.194C
Drug serum concentration [mcg/L, Median (IQR)]		8.3 (6.2-10.7)	14.6 (11.4-17.1)	< 0.001M
Antiepileptic therapy [(Frequency (%)]	Monotherapy	382 (52.9%)	148 (49.3%)	0.298C
	Polytherapy	340 (47.1%)	152 (50.7%)	

Table 4 demonstrates the comorbidities and chronic diseases linked with the longer usage of medicines in both the carbamazepine and phenytoin groups. Levetiracetam was the most recommended AED among both groups: 24% in the carbamazepine group and 26% in the phenytoin group. Additionally, aspirin (18% vs. 6.6%, p < 0.001), proton pump inhibitors (32.3% vs. 16.9%, p < 0.001), and metformin (17.3% vs 11.5%, p 0.012) were more common among the phenytoin group. Folic acid was prescribed as a long-term medication among both groups: 5.9% in the carbamazepine group and 6.7% in the phenytoin group. Comorbid conditions of neurological (29.3% vs. 17.1%, p< 0.001), hypertension (28.3% vs. 17.4%, p< 0.001), other CVD (11.7% vs 5.7%, p<0.001) and diabetes mellitus (26.0% vs. 14.2%, p< 0.001) were the most prevalent conditions among phenytoin groups.

Table 4: Chronic comorbid conditions and long-term medication use among both the carbamazepine and phenytoin groups.

Number of Subjects	Carbamazepine	Phenytoin	P Value
Number of Subjects	724	300	
Concomitant Medications ([Frequency (%)])			
Valproic acid	85 (11.7%)	44 (14.7%)	0.199C
Levetiracetam	174 (24%)	78 (26%)	0.506C
Lamotrigine	52 (7.2%)	13 (4.3%)	0.089C
Topiramate	63 (8.7%)	18 (6.0%)	0.145C
Lacosamide	50 (6.9%)	20 (6.7%)	0.890C
Phenobarbital	12 (1.7%)	10 (3.3%)	0.092C

[2]IQR: interquartile range; BMI: body mass index.
"*" indicates statistically significant difference, p values less than $^{0.05}$ indicates statistical significance. p values that were calculated with Mann-Whitney U test are indicated with superscript "M" while p values that were calculated with Person's Chi-square are indicated with superscript "C"

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Cont. Table 4

Number of Subjects	Carbamazepine	Phenytoin	P Value
Other Antiepileptic Drugs	4 (0.6%)	0 (0.0%)	0.327F
Antipsychotic/Antidepressants	129 (17.8%)	57 (19%)	0.655C
Aspirin	48 (6.6%)	54 (18%)	< 0.001C*
NSAIDS*	33 (4.6%)	20 (6.7%)	0.166C
Proton pump inhibitors	122 (16.9%)	97 (32.3%)	< 0.001C*
Metformin	83 (11.5%)	52 (17.3%)	0.012C*
ACEI*/Diuretics	88 (12.2%)	48 (16.0%)	0.099C
Multivitamin	103 (14.2%)	45 (15.0%)	0.749C
Vitamin D	234 (32.3%)	84 (28.0%)	0.174C
Calcium	99 (13.7%)	67 (22.3%)	0.001C*
Folic Acid	43 (5.9%)	20 (6.7%)	0.659C
Co-morbidities ([Frequency (%)])			
Neurological	124 (17.1%)	88 (29.3%)	< 0.001C*
Psychiatric	132 (18.2%)	60 (20.0%)	0.509C
Hypertension	126 (17.4%)	85 (28.3%)	< 0.001C*
Other CVD*	41 (5.7%)	35 (11.7%)	0.001C*
Diabetes Mellitus	103 (14.2%)	78 (26.0%)	< 0.001C*
Dyslipidemia	77 (10.6%)	104 (34.7%)	< 0.001C*
Asthma/COPD*	17 (2.3%)	10 (3.3%)	0.370C
Thyroid/Parathyroid	45 (6.2%)	32 (10.7%)	0.014C*
Osteoporosis/Osteoarthritis	26 (3.6%)	11 (3.7%)	0.935C
Urological Disorder	15 (2.1%)	13 (4.3%)	0.043C*
Chronic Pain	18 (2.5%)	11 (3.7%)	0.300C

Table 5 shows the treatment duration and dosage among the study participants. The Median (IQR) duration of treatment of the carbamazepine users was 5 (3-7) years, while phenytoin users were 5 (3-6) years. In the carbamazepine group, 39.0% of the participants received a regular dosage of 800 mg, and 32.6% received a daily dose of 400 mg. The remaining participants received a daily dose of 200 mg, 600 mg, 1000 mg, and 1200 mg. In addition, 93.7% of the participants in the phenytoin group received a daily dose of 300 mg.

Table 5: Duration of treatment and dosage among study participants

	Dosage	Carbamazepine	Phenytoin	P Value
Duration of treatment [Year, Median (IQR)]		5 (3-7)	5 (3-6)	0.004*
Total daily dosage (mg/day) [(Frequency (%)]	200	35 (4.8%)		
	300		281 (93.7%)	
	400	236 (32.6%)	19 (6.3%)	
	600	77 (10.6%)		
	800	282 (39.0)		
	1000	21 (2.9%)		
	1200	73 (10.1%)		

Table 6 illustrates the incidence and intensity of anaemia and haematological parameters of CBC among study participants. In the carbamazepine group of females, 64 patients (19.3%) had mild anaemia, 64 patients (19.3%) had moderate anaemia, and 7 patients (2.1%) had severe anaemia. While in the carbamazepine group of males, 42 patients (10.7%) had mild anaemia, 15 patients (3.8%) had moderate anaemia, and two patients (0.5%) had severe anaemia. Moreover, in the phenytoin group of females, 17 patients (13.8%) had mild anaemia, and 14 patients (11.4%) had moderate anaemia. In contrast, in the phenytoin group of males, 27 patients (15.3%) had mild anaemia, 13 patients (7.3%) had moderate anaemia, and one patient (0.5%) had severe anaemia. The phenytoin group demonstrated decreased median haemoglobin levels in contrast to the carbamazepine group of both male and female participants. A significant transformation has been found between the two groups. The Median (IQR) of haematological parameters, such as RBCs, HCT, MCH, and MCHC, was slightly lower among the phenytoin group. On the contrary, MCV was somewhat higher, 87.8 (83.9-91.1) fl, compared to the carbamazepine group, RBCs 4.7 (4.3-5.2) x106/µl, HCT 41.1 (37.8-44.4)%, MCV 87.4 (83.7-90.5)fl, MCH 29.3 (27.9-30.8), and MCHC 336 (326-343) gm/l, with no substantial alteration between the two groups.

Table 7 illustrates the significant relationship between the incidence of anaemia and male subjects treated with carbamazepine compared to male subjects treated

Table 6 Incidence and severity of anaemia outcomes and haematological parameters of CBC among study participants.

			Carbamazepine	**Phenytoin**	**P Value**
Number of Subjects			724	300	
Incidence of Anaemia [(Frequency (%)]	Male		59/393 (15%)	41/177 (23.2%)	0.018C*
	Female		135/331 (40.8%)	31/123 (25.2%)	0.002C*
	Total Cases		194/724 (26.8%)	72/300 (24%)	
Severity of Anaemia [(Frequency (%)]	Male	Severe	2/393 (0.5%)	1/177 (0.5%)	0.848F
		Moderate	15/393 (3.8%)	13/177 (7.3%)	
		Mild	42/393 (10.7%)	27/177 (15.3%)	
	Female	Severe	7/331 (2.1%)	0/123 (0.0%)	0.347F
		Moderate	64/331 (19.3%)	14/123 (11.4%)	
		Mild	64/331 (19.3%)	17/123 (13.8%)	
Hematological Parameters of CBC [Median (IQR)]	Hb (Male, g/l)	146 (136-155)	141 (130-152)	0.001M*	
	Hb (Female, g/l)	124 (111-133)	128 (119-136)	0.003M*	
	RBCs (x106/µl)	4.7 (4.3-5.2)	4.6 (4.2-5.0)	0.912M	
	HCT (%)	41.1 (37.8-44.4)	40.3 (37.0-43.3)	0.891M	
	MCV (fl)	87.4 (83.7-90.5)	87.8 (83.9-91.1)	0.100M	
	MCH (pg)	29.3 (27.9-30.8)	29.2 (28.0-30.7)	0.518M	
	MCHC (gm/l)	336 (326-343)	334 (326-341)	0.883M	
	WBCs (x103/µl)	6.3 (5.2-7.8)	6.9 (5.6-9.0)	< 0.001M*	
	Platelets (x103/µl)	268 (219-326)	267 (227-316)	0.459M	

[3]*NSAIDS: Non-steroidal anti-inflammatory drugs, *ACEI: Angiotensin-converting enzyme inhibitors; *CVD: Cardiovascular diseases, *COPD: chronic obstructive pulmonary diseases.
"*" indicates statistically significant difference, p values less than $^{0.05}$ indicates statistical significance. p values that were calculated with Fisher's exact test are indicated with superscript "F" while p values that were calculated with Person's Chi-square are indicated with superscript "C".

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with phenytoin COR = 0.586; 95% CI: (0.375-0.915) (p = 0.019). The multivariable logistic regression analyses showed no statistically significant relationship between the incidence of anaemia and male subjects treated with carbamazepine compared to male subjects treated with phenytoin (AOR = 0.787; 95% CI: 0.460-1.35) (p = 0.383). The results of univariate analyses revealed a significant relationship between the incidence of anaemia and female subjects treated with carbamazepine compared to male subjects treated with phenytoin COR = 2.04; 95% CI:1.29-3.25) (p = 0.002). The results of multivariable logistic regression analyses were in agreement with those of univariate analyses regarding female subjects treated with carbamazepine being 2.33 times (95% CI: 1.39-3.87) (p =0.001) more likely to have anaemia compared to females treated with phenytoin.

Table 7: Odds ratios for incidence of anaemia

	Gender	COR (95% CI)	P value for COR	AOR (95%CI)	P value for AOR
Incidence of Anaemia (Carbamazepine/ Phenytoin)	Male	0.586 (0.375-0.915)	0.019*	0.787 (0.460-1.35)	0.383
	Female	2.04 (1.29-3.25)	0.002*	2.33 (1.39-3.87)	0.001*

Table 8 illustrates the classification of anaemia regarding MCV and subgroups by gender. The normocytic anaemia was highest in both the groups and genders, which accounts for 66.1% in the male carbamazepine group and 75.6% in the male phenytoin group. The female carbamazepine group accounted for 63.7%, whereas the female phenytoin group 51.6%. In the microcytic anaemia proportion, the male carbamazepine group accounted for 30.5%, while the male phenytoin group 22%. The female carbamazepine group was 35.6%, and the female phenytoin group was 48.4%. The lowest proportion was related to macrocytic anaemia; the male carbamazepine group was 3.4%, the male phenytoin group was 2.4%, and the female carbamazepine group was 0.7%, with no significant difference between both groups and both genders in all types of anaemia.

Table 8: Types of Anaemia based on the main corpuscular volume (MCV)

	Gender	Types	Carbamazepine	Phenytoin	P value
Types of Anaemia based on MCV [(Frequency (%)]	Male	Microcytic	18/59 (30.5%)	9/41 (22%)	0.619F
		Normocytic	39/59 (66.1%)	31/41 (75.6%)	
		Macrocytic	2/59 (3.4%)	1/41 (2.4%)	
	Female	Microcytic	48/135 (35.6%)	15/31 (48.4%)	0.367F
		Normocytic	86/135 (63.7%)	16/31 (51.6%)	
		Macrocytic	1/135 (0.7%)	0/31 (0.00%)	

Table 9 demonstrated a significant correlation between phenytoin plasma concentration and the incidence of anaemia in female subjects (p =0.002). In contrast, there was no substantial association between the occurrence of anaemia and carbamazepine serum concentration in both genders and phenytoin plasma concentration in male subjects.

[5]CBC: complete blood count; Hb: hemoglobin; RBCs: red blood corpuscles; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration—WBCs: white blood cells.
"*" indicates a statistically significant difference, and p less than $^{0.05}$ indicates statistical significance. p values that were calculated with Fisher's exact test are indicated with superscript "F"; p values that were calculated with Person's Chi-square are indicated with superscript "C." In contrast, p values that were calculated with the Mann-Whitney U test are indicated with superscript "M".

[6]COR: crude odd ratio; AOR: adjusted odd ratio; CI: confidence intervals; AOR: adjusted odds ratios.
"*" indicates a statistically significant difference, and p less than $^{0.05}$ indicates statistical significance.

Table 9: Correlation between drug serum level and the incidence of anaemia

Drug serum level				
			Correlation Coefficient	P value
Incidence of Anaemia	Carbamazepine	Male	0.005	0.943
		Female	0.037	0.622
	Phenytoin	Male	0.079	0.438
		Female	0.351	0.002*

Table 10 shows that both groups had generalized epilepsy in common, including both male and female participants, followed by other kinds: focal and combined. No statistically significant relationship with anaemia was indicated in both groups.

Table 10: Association between types of epilepsy and the incidence of anaemia

Types of epilepsy					
			Types	[(Frequency (%)]	Association P value
Incidence of Anaemia	Carbamazepine	Anemic male	Focal	16/57 (28.1%)	0.244F
			Generalized	34/57 (59.6%)	
			Combined	7/57 (12.3%)	
			Unknown	0/57 (0.0%)	
		Anemic Female	Focal	38/124 (30.6%)	0.247F
			Generalized	73/124 (58.9%)	
			Combined	13/124 (10.5%)	
			Unknown	0 (0.0%)	
	Phenytoin	Anemic male	Focal	6/38 (15.8%)	0.153F
			Generalized	29/38 (76.3%)	
			Combined	2/38 (5.3%)	
			Unknown	1/38 (2.6%)	
		Anemic Female	Focal	6/25 (24%)	0.807F
			Generalized	18/25 (72%)	
			Combined	1/25 (4%)	
			Unknown	0/25 (0.0%)	

Table 11 illustrates no significant association between folic acid supplementation and the prevalence of anaemia in the phenytoin-treated females. In carbamazepine-treated males, a positive correlation was found between folic acid supplementation and anaemia occurrence. There was no significant association between folic acid supplementation and the incidence of anaemia in the phenytoin-treated males. A positive connection exists between folic acid supplementation and becoming anaemic in carbamazepine-treated females. Six of 14 female subjects were anaemic while taking folic acid supplements in the phenytoin group.

[7]MCV: mean corpuscular volume.

"*" indicates a statistically significant difference, and p less than $^{0.05}$ indicates statistical significance. p values were calculated with Fisher's exact test and indicated with superscript "F."

[8]"*" indicates a statistically significant difference, and p less than $^{0.05}$ indicates statistical significance.

[9]"*" indicates a statistically significant difference, and p less than $^{0.05}$ indicates statistical significance. p values were calculated with Fisher's exact test and indicated with superscript "F".

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Table 11: Association between folic acid supplementation and the incidence of anaemia

Folic acid supplementation				
			[(Frequency (%)]	Association P value
Incidence of Anaemia	Carbamazepine	Anemic Male	5/8 (62.5%)	0.003F*
		Anemic Female	25/35 (71.4%)	< 0.001C*
	Phenytoin	Anemic Male	3/6 (50%)	0.138F
		Anemic Female	6/14 (42.9%)	0.106C

Discussion

Anaemia in adults is defined as haemoglobin levels <120 g/l in women and <130 g/l in men. The WHO categorized the severity of Anemia based on blood hemoglobin level for women as mild Anemia: 110-119 g/l, moderate Anemia: 80-109 g/l, and severe anemia: lower than 80 g/l, and for men mild Anemia: 110-129 g/l, moderate Anemia: 80-109 g/l, and severe Anemia: lower than 80 g/l [36]. Based on the data from routine clinical practice, this is the first retrospective study that evaluated and associated the incidence of anaemia between carbamazepine and phenytoin in the KSA. The study classified the severity of anaemia by retrieving the CBC results from a hospital-based database. Carbamazepine was more commonly prescribed than phenytoin in this study, consistent with the international findings that carbamazepine is more widely prescribed in Western regions due to side effects associated with phenytoin. In contrast, phenytoin is still commonly used in developing countries worldwide because of its low cost [38].

However, in the KSA, updated information regarding AEDs that were commonly prescribed and used was not available and needed to be updated. Moreover, the most recent and available evidence demonstrated no difference between these two drugs for treatment outcomes and side effects as monotherapy [11]. The highest incidence of anaemia in both groups was mild anaemia, followed by moderate anaemia, and a few subjects were severely anaemic. In medical practice, those experiencing mild to moderate anaemia are more likely to receive medical treatment [39]. Many participants with mild to moderate anaemia in the present study did not receive treatment. In contrast, the medical staff focus on disorders other than anaemia as a possible side effect of a hospital visit. However, if the anaemia patient is left untreated for an extended period, the consequences and complications can become more severe [39].

This study showed an association between females treated with carbamazepine and phenytoin and the incidence of anaemia. The study found a correlation between phenytoin plasma levels for female subjects and the incidence of anaemia. In addition, based on the AOR, female subjects treated with carbamazepine were 2.33 times more likely to have anaemia compared to females treated with phenytoin. Gender issues associated with pharmacodynamics and pharmacokinetics, the influence of female-specific concomitant therapy with drugs involved in a pharmacokinetic interaction, and CYP3A substrates were more prevalent in women than in men [40].

Few cases of macrocytic anaemia were consistent with other results regarding folic acid supplementation. Furthermore, the occurrence of anaemia in this study was not considered folic acid deficiency anaemia as a potential contributing factor for anaemia. The findings of this study showed that normocytic anaemia was the most usual kind of anaemia found in the patients. That means the causes of anaemia may be related to other types, such as hemolytic anaemia, vitamin B12 deficiency anaemia, and iron deficiency anaemia. In the literature, many reported cases linked the AEDs to different kinds of anaemia. Further observational studies and clinical trials are necessary to prove an explicit association and causation between AEDs and anaemia.

Strengths, Limitations and Recommendations

The study's strength lies in the statement that this retrospective study is the first to compare and evaluate the incidence of anaemia between two AEDs in Saudi Arabia. The study has compared the occurrence of anaemia and significant changes in the haematological parameters of the CBC between patients taking carbamazepine and those taking phenytoin. The study highlights two of the most widely recommended AEDs in the treatment of epilepsy. However, the study has some limitations, including the retrospective nature of the data collected from electronic

[10]"*" indicates a statistically significant difference, and p less than [0.05] indicates statistical significance. p values calculated with Fisher's exact test are indicated with superscript "F," while p values calculated with the Chi-square test are indicated with superscript "C."

medical records. The participants' medication adherence or dietary iron consumption is unavailable. The plasma level of phenytoin used in this study was the total.
Further multi-centre observational and clinical trials are necessary to prove an explicit association and causation between AEDs and anaemia. A more extensive prospective study could involve supplementary variables to ensure the accessibility of measures for all subjects and include a longer observation period. There is a need for more comprehensive research on mechanisms and the pathogenicity of anaemia caused by AEDs. Moreover, studies are required to overcome the anaemic drawbacks of AEDs and find the proper treatment and strategies to prevent anaemia.

Conclusion

Carbamazepine and phenytoin were the cornerstones of treatment for epilepsy, which potentially causes anaemia as a side effect. In the therapy of epilepsy, routine CBC monitoring becomes essential with an appropriate treatment plan to prevent anaemia in epileptic patients. The outcomes are beneficial for healthcare decision-makers and patients to understand the type and risk factors of anaemia. The highest incidence of anaemia was mild, and normocytic anaemia was the most common type among the two drugs.

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