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Phenytoin blood levels and their relationship with physiological and demographic factors: A retrospective analysis of gender, age, and drug interactions

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Abstract

Phenytoin, a first-generation antiepileptic drug, requires therapeutic blood levels between 10–20 µg/mL for efficacy. Maintaining this range poses challenges. This study investigated the effects of gender, age, chronic diseases, and concomitant medications on phenytoin blood levels in epilepsy patients. In this retrospective study, data from 142 epilepsy patients on phenytoin therapy were analyzed to evaluate the effects of physiological factors (gender, age, and chronic diseases) and pharmacological factors (drug interactions) on phenytoin blood levels. Blood concentrations were categorized as therapeutic (10–20 µg/mL), subtherapeutic (<10 µg/mL), or toxic (>30 µg/mL). Statistical analysis included descriptive statistics, Kruskal-Wallis, Mann-Whitney U, Chi-square, and Spearman's correlation tests (SPSS 27.0). Ethical approval was obtained from the Biruni University Scientific Research Ethics Committee. Of the 142 patients, 66.9% were male, and 33.1% were female, with a mean age of 62.17 years. Subtherapeutic levels were found in 81% of patients, while 12.7% had therapeutic and 6.3% had above-therapeutic levels. Among those with above-therapeutic levels, 77.8% exhibited drug interactions. Mean phenytoin levels were significantly higher in females than males ($p<0.05$) but lower in patients with drug interactions ($p<0.05$). No significant correlation was found between chronic diseases and phenytoin levels. Patients in intensive care units had higher levels than other groups ($p<0.05$). Phenytoin blood levels are influenced by gender, age, chronic diseases, and drug interactions. Individualized therapy and regular monitoring are essential to optimize seizure control and minimize toxicity. Future studies with larger cohorts are needed to validate these findings and improve phenytoin management.

Keywords: Phenytoin, drug monitoring, age, gender, drug interaction

Introduction

Phenytoin (PHT) is a first-generation antiepileptic drug commonly used as monotherapy for patients with epilepsy. Synthesized as diphenylhydantoin in 1908 by the German chemist Heinrich Biltz, phenytoin was identified in 1936 to be effective against seizures [1]. Over the past 90 years, PHT has been extensively studied in neuropharmacology, not only for epilepsy but also for wound healing, bipolar disorder, various types of ulcers, and as a neuroprotective agent in multiple sclerosis [2-4]. Phenytoin is effective against focal and generalized tonic-clonic seizures [5] by binding to neurotransmitter receptors and blocking ion channels, as well as inhibiting the reuptake or metabolism of certain neurotransmitters [6].

For phenytoin to exert its therapeutic effect in seizure management, drug concentrations must be maintained between 10–20 µg/mL. Levels ≥30 µg/mL are considered toxic, and levels ≥100 µg/mL may be fatal [7]. However, certain characteristics of PHT make it challenging to maintain blood concentrations within the therapeutic range. First, phenytoin has a narrow therapeutic index, reported to be around 2 in a 2016 study [8], increasing the likelihood of side effects and necessitating regular therapeutic drug monitoring. Furthermore, about 90%

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of circulating phenytoin is bound to plasma proteins (primarily albumin), rendering only about 10% free and pharmacologically active. In specific conditions such as neonatal status, pregnancy, hypoalbuminemia (as seen in renal or hepatic insufficiency, or malnutrition), or uremia, the free (active) fraction of phenytoin increases. Consequently, patients with reduced protein-binding capacity may exhibit signs of toxicity despite having normal phenytoin blood concentrations [9].

In addition, phenytoin demonstrates nonlinear kinetics, whereby minor dose alterations can lead to significant changes in blood concentration. Because it is metabolized by cytochrome P450 (CYP450) hepatic enzymes, it is prone to numerous drug interactions [9,10]. Phenytoin's pharmacokinetics, and thus its blood concentration, can also be influenced by physiological factors such as age, gender, and chronic diseases [11]. Similar to many drugs metabolized by cytochrome P450 enzymes, phenytoin exhibits pharmacokinetic and/or pharmacodynamic differences between males and females. During pregnancy, menopause, or post-menopause in women, phenytoin therapy can be affected by hormonal fluctuations that influence the enzymatic system [10]. Moreover, age-related reductions in CYP450 activity and changes in drug absorption, distribution, metabolism, and excretion can impact phenytoin blood levels. In elderly patients, decreased gastric secretion, blood flow, and gastrointestinal motility can reduce drug absorption, while lower serum albumin levels increase the free drug fraction. In children, phenytoin metabolism is faster than in adults, whereas older adults experience a gradual decline in phenytoin clearance.

Epilepsy is the fourth most common neurological disorder, accounting for approximately 1% of all emergency department visits related to seizures [12]. In a multicenter study examining the emergency management of patients presenting with seizures, phenytoin emerged as the most frequently used antiepileptic drug [13].

These pharmacological properties render phenytoin management complex, necessitating regular patient monitoring. Accordingly, this study aimed to evaluate the influence of physiological factors (e.g., gender, age, and chronic diseases) and the pharmacological effects of co-administered medications on phenytoin levels in epilepsy patients presenting to emergency departments and outpatient clinics while undergoing phenytoin therapy.

Material and Methods

Data Source

In this retrospective study, data were obtained from the medical records of 142 epilepsy patients who presented to Kırklareli Training and Research Hospital between January 1 and December 31, 2023. All patients included were on phenytoin therapy and had documented phenytoin blood measurements.

The following variables were recorded for the dataset: phenytoin blood level, gender, age, chronic diseases, and concomitant medications. The department or clinic to which the patient presented was also noted. Inclusion criteria were: (1) a confirmed diagnosis of epilepsy, (2) documented use of phenytoin, (3) phenytoin blood level measurements prior to study initiation, and (4) age ≥18 years. Individuals under 18, patients using phenytoin without having a phenytoin level measured, and patients lacking complete information on chronic diseases or current medications were excluded from the study.

This study was conducted with the approval of the Biruni University Scientific Research Ethics Committee (12/12 2024, No: 2024-BIAEK/05-01).

Phenytoin Determination

Phenytoin blood levels ranging between 10–20 µg/mL were defined as the therapeutic range. Levels below 10 µg/mL were defined as subtherapeutic, while those above 20 µg/mL were defined as above the therapeutic range. Concentrations ≥30 µg/mL were considered toxic [7]. Phenytoin levels were measured using a turbidimetric method on a ROCHE COBAS C503 device.

Phenytoin-Drug Interaction Analysis

A record was made of all concomitant medications taken by the patients alongside phenytoin. The potential interactions between these medications and phenytoin were evaluated using multiple drug-interaction databases, including Drugs.com, DrugBank, Medscape, and WebMD. Concomitant drugs were classified as either interacting or non-interacting with phenytoin.

Classification of Chronic Diseases

For the purposes of this study, the chronic diseases present in patients with epilepsy were classified as follows (Table 1).

Table 1. Classification of chronic diseases

Terms of chronic diseases	Classification
Neurological diseases	1
Cardiovascular diseases	2
Endocrine diseases	3
Pulmonary diseases	4
Cancer	5
Psychiatric disorders	6
No chronic disease	0

Statistical Analysis

Descriptive statistics (mean, standard deviation, median, minimum, maximum, frequency, and percentage) were calculated. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess data distribution. For non-normally distributed independent quantitative variables, the Kruskal-Wallis and Mann-Whitney U tests were employed. For categorical variables, the Chi-square test or Fisher's exact test (when Chi-square assumptions were not met) was used. Spearman's correlation was applied for correlation analysis. All statistical analyses were performed using SPSS version 27.0, with a significance threshold set at $p<0.05$.

Results

The study evaluated 142 epilepsy patients undergoing phenytoin therapy. Of these, 66.9% (n=95) were male and 33.1% (n=47)

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were female. The mean age of the total sample was 62.17±19.31 years, with 59.8±18.78 years in males and 66.97±19.69 years in females (Table 2). The age range was 30–97 years among females and 22–94 years among males. No significant difference was observed in patient age among the subtherapeutic, therapeutic, and above-therapeutic phenytoin groups ($p>0.05$), and no significant correlation was detected between mean phenytoin concentration and age ($p>0.05$).

Regarding phenytoin blood levels, 115 out of 142 patients (81%) had subtherapeutic levels (mean 3.48±2.48 µg/mL), including 32 females and 83 males. The proportion of female patients in the subtherapeutic group was significantly lower than that in other groups ($p<0.05$). Only 18 patients (12.7%) demonstrated therapeutic phenytoin levels (10–20 µg/mL), with a mean concentration of 13.42±2.96 µg/mL; of these, 7 were female and 11 were male. Nine patients (6.3%) exhibited above-therapeutic phenytoin levels (mean 28.01±12.06 µg/mL), including 8 females and 1 male (Table 3). Two female patients had toxic phenytoin blood levels (>30 µg/mL): one 42-year-old patient taking levetiracetam, carbamazepine, valproic acid, and fluoxetine, who was referred from the emergency department to the neurology clinic with a level of 58.8 µg/mL; and one 90-year-old intensive care patient on amiodarone and a macrolide antibiotic, with a level of 31.9 µg/mL. Overall, mean phenytoin concentrations were significantly higher in females compared to males ($p<0.05$) (Table 4).

As shown in Table 3, 42 patients had no accompanying chronic diseases, while 100 had one or more chronic diseases, with cardiovascular disorders being the most common (72 patients). Additionally, 37 patients had other neurological disorders, 12 had endocrine disorders, 4 had cancer, 2 had psychiatric conditions, and 2 had pulmonary diseases. No significant correlation was identified between the presence of chronic diseases and phenytoin levels.

Analysis of drug interactions revealed that 71 patients were receiving medications that interact with phenytoin, 34 patients were taking non-interacting medications, and 37 patients were not on any additional medications. Mean phenytoin concentrations were significantly lower in the group with identified drug interactions ($p<0.05$) (Table 4). Among the 18 patients who had therapeutic phenytoin levels, 3 had drug interactions, 11 did not, and 4 were on no additional medications. Of the 9 patients with above-therapeutic levels, 7 had phenytoin-drug interactions, 1 had no interaction, and 1 was on no other medications. Comparisons among the phenytoin-level groups showed that patients with therapeutic or above-therapeutic levels had significantly lower rates of drug interactions than those in the subtherapeutic group ($p<0.05$) (Table 3).

An analysis of mean phenytoin levels across different clinical settings revealed that patients admitted to the intensive care unit had significantly higher levels than those managed in other departments ($p<0.05$). Furthermore, among patients in other departments, mean phenytoin concentrations were also significantly higher than those in the emergency department ($p<0.05$) (Table 4).

The distribution of interactions between phenytoin and the medications used by the patients, as well as the potential effects of these interactions, are presented in Table 5, focusing on the five most frequently observed interactions in this study population.

Table 2. General characteristics of the patients

		Min-Max	Median	Mean±SD / n-%	
Age		22.0-97.0	60.0	62.1±19.3	
Gender	**Female**			47	33.1
	Male			95	66.9
Phenytoin blood level	**Below the therapeutic range**			115	81.0
	Within the therapeutic range			18	12.7
	Above the therapeutic range			9	6.3
Chronic disease	**(-)**			42	29.6
	(+)			100	70.4
***Chronic disease group**					
Neurological				37	26.1
Cardiovascular				72	50.7
Endocrine				12	8.5
Pulmonary				2	1.4
Cancer				4	2.8
Psychiatric				2	1.4
Drug interaction	**(-)**			34	23.9
	(+)			71	50.0
	No medication use			36	25.4

Min-Max: minimum-maximum, SD: standard deviation, n-%: sample size and percentage, *Disease with treatment duration longer than 6 months

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Table 3. Quantification of phenytoin in patients stratified according to the therapeutic level

		Below the therapeutic range (n=115)			Within and above the therapeutic range (n=27)			p
		Mean±SD	n (%)	Median	Mean±SD	n (%)	Median	
Age		62.2	19.4	60.0	62.1	19.3	60.0	0.930[m]
Gender	**Female**	32	27.8		15	55.6		**0.006**[X²]
	Male	83	72.2		12	44.4		
Chronic disease	**(-)**	34	29.6		8	29.6		0.995[X²]
	(+)	81	70.4		19	70.4		
Chronic disease group								
Neurological		29	25.2		8	29.6		0.638[X²]
Cardiovascular		58	50.4		14	51.9		0.895[X²]
Endocrine		11	9.6		1	3.7		0.324[X²]
Pulmonary		2	1.7		0	0.0		1.000[X²]
Cancer		4	3.5		0	0.0		1.000[X²]
Psychiatric		2	1.7		0	0.0		1.000[X²]
Drug drug interaction	**(-)**	22	26.5		12	54.5		**0.012**[X²]
	(+)	61	73.5		10	45.5		

m: Mann-Whitney U Test, X²: Chi-Square Test (Fischer's Exact Test), SD: standard deviation

Table 4. Evaluation of patient data based on mean phenytoin blood levels

		Phenytoin blood level			p
		Min-Max	Median	Mean±SD	
Gender	**Female**	0.1-58.8	5.2	9.4±11.1	**0.036**[m]
	Male	0.1-23.3	3.7	4.7±4.3	
Follow-up department	**[1]Emergency department**	0.1-20.3	2.9[23]	3.5±3.4	**0.000**[K]
	[2]Other departments	0.1-58.8	4.8[3]	7.3±8.6	
	[3]Intensive care unit	0.8-31.9	9.8	12.3±9.7	
Chronic disease	**(-)**	0.1-27.0	4.0	6.4±7.1	0.751[m]
	(+)	0.2-58.8	4.3	6.3±7.8	
Drug drug interaction	**(-)**	0.1-22.5	6.0	7.3±5.5	**0.025**[m]
	(+)	0.2-58.8	3.6	6.3±9.1	

K: Kruskal-Wallis Test (Mann-Whitney U Test), m: Mann-Whitney U Test , Min-Max: minimum-maximum, SD: standard deviation

Table 5. Evaluation of the five most frequent phenytoin–drug interactions observed in this study

Drug	Interaction level	Number of patients (n)	Potential effect
Acetylsalicylic acid (ASA)	Minor	15	Salicylates may displace phenytoin from plasma protein-binding sites
Amlodipine	Major	12	The metabolism of Phenytoin can be altered
Carbamazepine	Moderate	11	The serum concentration of Phenytoin can be decreased
Clopidogrel	Minor	8	The serum concentration of Phenytoin can be decreased
Valproic acid	Moderate	7	The serum concentration of Phenytoin can be decreased

Discussion

Phenytoin has long been under clinical neuropharmacological evaluation and serves as a primary antiepileptic agent for both focal and generalized tonic-clonic seizures. First synthesized by the German chemist Heinrich Biltz in 1908, it was found in 1936 to be beneficial in seizure control [14]. Due to certain pharmacological properties, phenytoin requires routine therapeutic drug monitoring. Accordingly, this study investigated the effects of physiological factors such as gender, age, and chronic diseases, as well as the pharmacological impact of concomitant medications, on phenytoin blood levels in epilepsy patients presenting to the emergency department and other outpatient clinics who were on phenytoin therapy.

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An analysis of the gender distribution among the patients in this study indicates that phenytoin was prescribed more frequently to males than to females, which may be explained by multiple factors. From the literature, even early investigations have reported notable side effects of phenytoin, particularly in women. For instance, a 1999 study suggested that, because of cosmetic-dermatological adverse effects, phenytoin should not be used as the first choice in epileptic women—except under emergency circumstances—as these side effects can be more socially disabling than the seizure disorder itself [15]. Furthermore, long-term phenytoin therapy can induce osteoporosis, especially in postmenopausal women [16]. These factors could explain why phenytoin was prescribed more frequently to men in our patient population.

There is no strict age limit for phenytoin use; the drug is administered across various age groups, including pediatric, adult, and geriatric patients. However, dosage requirements and side effect profiles may differ according to age. In particular, older patients may require closer phenytoin-level monitoring because of reduced hepatic metabolism [17]. In this study, 142 patients aged 22 to 97 years were included, and their mean age was 62.17 years. Notably, only 18 of these 142 patients were found to have therapeutic phenytoin levels, highlighting the importance of more intensive monitoring in older populations.

Among the elderly, reductions in hepatic and renal function, lower albumin levels, and comorbidities may alter the metabolism and distribution of phenytoin; hence, regular drug-level monitoring is considered even more critical in this group [10].

Analysis of phenytoin level data revealed that 115 out of 142 patients had subtherapeutic levels, suggesting potentially reduced treatment efficacy and an increased likelihood of inadequate seizure control. The mean phenytoin level in these patients was 3.48±2.48 μg/mL, indicating that many were below the desired therapeutic range. In such cases, dose adjustment, evaluation of potential drug interactions, or assessment of bioavailability may be necessary. Interestingly, the proportion of female patients with subtherapeutic phenytoin levels was significantly lower ($p<0.05$) than in the other groups, implying that women may be less likely than men to have subtherapeutic levels. This finding suggests potential gender-related differences in phenytoin metabolism or in dosing and therapeutic response. Although men constituted the majority of the patient population, only 11 reached the therapeutic range, while 7 of the 18 patients with therapeutic levels were female. This observation raises the possibility that males may have suboptimal dosing, drug metabolism, or treatment adherence. Moreover, 9 patients (8 women, 1 man) displayed phenytoin levels above the therapeutic range (mean 28.01±12.06 μg/mL), indicating a higher tendency among women to exceed therapeutic concentrations. The detection of toxic levels (>30 μg/mL) in two female patients further underscores the importance of monitoring potential toxicity in this subgroup. Gender-related pharmacokinetic and pharmacodynamic differences likely play a pivotal role in phenytoin therapy, potentially stemming from hormonal factors or variations in body composition. Notably, alterations in CYP450 enzyme activity are considered among the primary contributors to metabolic differences between men and women [10,18]. Overall, these findings highlight the necessity of individualized phenytoin dosing strategies that account for gender-specific variables.

Failure to maintain phenytoin in the desired therapeutic range can compromise seizure control and elevate toxicity risk, ultimately contributing to increased morbidity and mortality in epilepsy management [9].

Patients with epilepsy often present with multiple comorbidities and health issues. In this study, 72 of the 142 patients had cardiovascular disease, making it the most frequent chronic disorder accompanying epilepsy. Recent epidemiologic and mechanistic research has drawn attention to cardiac involvement in epilepsy, leading to the concept of the "epileptic heart" [19]. Neurological disorders and endocrine diseases were also identified as significant comorbid conditions. Nonetheless, no significant correlation emerged between phenytoin levels and the presence of chronic diseases, suggesting that comorbidities may not directly affect phenytoin concentrations.

Like many other antiepileptic drugs, phenytoin is closely associated with CYP450 enzymes. It has been shown to induce CYP2C9, CYP2C19, and CYP3A4 [20]. By inducing this enzymatic system, phenytoin accelerates the metabolism of a wide range of drugs, including other antiepileptics, oral contraceptives, corticosteroids, digitalis agents, theophylline, quinidine, doxycycline, cyclosporine, mexiletine, methadone, verapamil, levodopa, and muscle relaxants. Conversely, medications that interact with phenytoin may alter its metabolism, clearance, or binding capacity, leading to changes in its plasma concentration [9]. In our investigation of the 142 patients, 71 (50%) were taking concomitant medications that interacted with phenytoin, 34 (23.9%) were on non-interacting drugs, and 37 were not on any other medication. Comparing phenytoin-level categories, patients who were within or above the therapeutic range exhibited significantly fewer drug interactions than those with subtherapeutic levels ($p<0.05$, Table 3). This result implies that subtherapeutic phenytoin levels may be associated with a higher incidence of drug interactions, potentially adversely affecting therapeutic efficacy. Consistent with this, mean phenytoin concentrations were significantly lower in the group with identified drug interactions. Such reductions in phenytoin levels might result from drugs that increase its metabolic rate—such as carbamazepine, rifampin, or phenobarbital—thereby expediting phenytoin clearance and lowering plasma concentrations [21].

Among patients exhibiting toxic phenytoin levels, one female patient, whose phenytoin concentration reached 58.8 μg/mL, was simultaneously taking levetiracetam, carbamazepine, valproic acid, and fluoxetine. The phenytoin–carbamazepine interaction has long been known to potentially raise phenytoin

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concentrations to toxic levels while decreasing carbamazepine to subtherapeutic levels [22]. Similarly, valproic acid has a complex effect; it increases the free fraction of phenytoin—thereby enhancing clearance—yet also inhibits phenytoin metabolism, overall elevating phenytoin levels [23]. Fluoxetine can likewise increase plasma phenytoin concentrations, potentially leading to toxicity [24]. Another patient with toxic phenytoin levels was receiving amiodarone, which is known to reduce phenytoin metabolism and thus elevate its plasma concentration [25]. That patient was also on a macrolide antibiotic. A 1997 study in rats found that macrolide antibiotics (erythromycin, clarithromycin, and roxithromycin) raised phenytoin's area under the plasma concentration–time curve, maximum plasma concentration, and elimination half-life (t½), while reducing cytochrome P-450 levels [26]. These observations suggest that drug-drug interactions contributed to both patients' toxic phenytoin levels in our study, underscoring the potential hazards of co-administering such agents with phenytoin and the need for regular level monitoring.

When mean phenytoin concentrations were evaluated by clinical setting, patients presenting to the emergency department showed lower mean phenytoin levels. This finding suggests that subtherapeutic phenytoin levels may have predisposed them to seizure activity. Notably, regaining seizure control and adjusting phenytoin doses in the emergency department, followed by discharge, indicates effective management. However, the higher mean phenytoin levels in patients admitted to intensive care units raise concern about possible phenytoin toxicity.

Given phenytoin's narrow therapeutic index and extensive drug-interaction potential, both routine monitoring and investigation of pharmacogenetic factors may play pivotal roles in optimizing individualized dosing [8].

Limitations

One limitation of this study is that it was conducted at a single center, which may restrict the generalizability of the findings. Additionally, the retrospective nature of the data collection resulted in incomplete information regarding drug doses or treatment durations. Moreover, it was not feasible to thoroughly evaluate patient compliance or lifestyle factors that could have influenced the results.

Conclusion

This study explored the influence of physiological factors, including gender, age, and chronic diseases, as well as concomitant medications, on phenytoin blood concentrations in patients with epilepsy. The findings highlight significant variability in phenytoin therapy influenced by these factors, underscoring the importance of personalized treatment approaches. Regular therapeutic drug monitoring, tailored to account for physiological differences and potential drug interactions, is crucial for optimizing phenytoin therapy. Future research involving larger patient cohorts could provide deeper insights, further improving the clinical management of phenytoin treatment.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This study was conducted with the approval of the Biruni University Scientific Research Ethics Committee (12/12 2024, No:2024-BIAEK/05-01).

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