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Article

Clinical Importance of Phenytoin Monitoring to Reduce Phenytoin-Related Toxicity in Saudi Patients with Epilepsy

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Abstract:

Background: Phenytoin toxicity can result from overdose, dosage changes, drug interac-tions, or physiological alterations. Symptoms range from nausea and confusion to severe cases involving coma and seizures, though fatalities are rare. To date, no literature has been found concerning phenytoin monitoring in Saudi epileptic patients. This study is the first to inves-tigate phenytoin monitoring for toxicity prevention, optimal dosing, and adverse effect management in Saudi epileptic patients. **Methods**: A two-month, randomized, open-label, prospective monitoring study was conducted in Saudi epileptic patients treated with phen-ytoin. The patients (n=40) were subdivided into two groups (monitored and unmonitored) to check the prevalence of phenytoin toxicity after two months of monitoring. **Results**: Most patients' current dose was 100 mg TID: 65% and 55% in the monitored and unmonitored groups, respectively. Statistical analysis showed significant differences between current doses of the patients in the monitored (P=0.010) and unmonitored groups (P=0.018). In addition, there was a significant difference between serum levels of phenytoin regarding the monitored and unmonitored groups in the first month and second month (P=0.0246 and P=0.04), respectively. Further, there was no significant difference between the kidney functions in the first second months in the monitored group (P=0.077), while there was a substantial difference in the unmonitored group (P=0.0241). Moreover, a significant dif-ference between the monitored and unmonitored groups in the first and second months for serum creatinine (P<0.001 and P=0.032) was recorded. **Conclusions**: The current study reports that continuous phenytoin monitoring in Saudi epileptic patients reduces the incidence of phenytoin toxicity. Toxicity was observed in 5% of monitored patients compared to 15% of unmonitored patients.

Keywords: Phenytoin, Saudi Epileptic Patients, Monitoring, Toxicity

Introduction

The introduction in 1939, the Food and Drug Administration approved phenytoin to treat epilepsy[1] . Phenytoin has proven effective in treating generalized tonic-clonic seizures, complex partial seizures, status epilepticus, trigeminal neuralgia, and behavior disorders. In the USA, phenytoin represents approximately 52% of all prescribed anti-epileptic drugs (AEDs) compared with 19% for valproic acid, 11% for carbamazepine, and 7% for phenobarbital[2]. Phenytoin was previously indicated to treat arrhythmia, digoxin toxicity, and tricyclic antidepressant toxicity; it is now only used as an AED[3]. Phenytoin is known chemically as 5,5-diphenyl-2,4-thiazolidinedione with an empirical formula of C15H12N2O2 Fig. 1. Phenytoin has a molecular weight of 252.26 for the free acid and a molecular weight of 274.25 for the sodium salt, which is equivalent to an acid content of 91.98%[4].

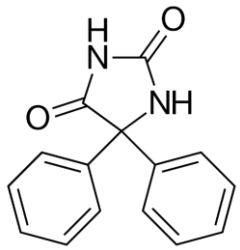

Fig. 1: Chemical structure of phenytoin (5)**.**

Phenytoin poisoning can occur following various circumstances, whether intentional, such as drug overdose, dosage adjustments, or drug interactions, or unintentional, such as changes in body physiology. Phenytoin overdose displays nausea and central nervous system dysfunction (particularly confusion, nystagmus, and ataxia), with a depressed conscious state, coma, and seizures associated with more severe cases [1, 5] Arrhythmias and hypotension are less frequently associated with phenytoin overdose; however, they are more commonly associated with intravenous administration of phenytoin or with fosphenytoin. Deaths rarely occur in sole phenytoin ingestion[6, 7]. The control of symptoms is usually symptomatic, including considering vital functions, managing nausea and vomiting, and avoiding injuries due to confusion and ataxia. Unfortunately, no antidote for phenytoin intoxication exists, and no indication has been detected regarding any method of gastrointestinal decontamination or improved elimination[8]. Activated charcoal could be used in early incidence. Plasmapheresis, hemodialysis, and hemoperfusion have not been proven effective in managing phenytoin intoxication [9]

Narrow therapeutic index (NTI) drugs are characterized by a small difference between therapeutic and toxic doses, making precise dosing critical. Even minor deviations in drug concentrations can result in therapeutic failure or toxicity, requiring careful monitoring of blood or plasma levels through therapeutic drug monitoring (TDM) [10]. These drugs also exhibit low-to-moderate within-subject variability, usually not exceeding 30%, which emphasizes the need for consistent pharmacokinetic and pharmacodynamic behavior. In clinical practice, NTI drugs are dosed with small adjustments, often less than 20%, to maintain safety and efficacy. Additionally, bioequivalence standards for generic versions of NTI drugs are stricter than for non-NTI drugs, involving reference-scaled testing and variability comparisons to ensure they closely match the brand-name formulations in both safety and therapeutic effect [11, 12].

Many clinical trials have suggested that the therapeutic index of phenytoin was two[13, 14]. Unfortunately, no substantial evidence has been detected regarding phenytoin's safety profile, either as monotherapy or adjunctive therapy[7]. In one meta-analysis, phenytoin efficacy, whether used alone or in combination therapy, was evaluated using three different measures: a. percentage of patients who had a >50% reduction, b. reduction in total seizures during the study period, and c. percentage of patients with seizure freedom in a specific period. The results revealed that the identified therapeutic range of phenytoin was 10–20 μg/mL. However, the dose ranges connected with effectiveness and toxicity overlap moderately. Seizure incidence was dose-related, and seizure control was usually poor at concentrations less than 10 μg/mL.70–74, while serum concentrations between 15 and 20 were associated with better seizure control. A dose of 10–20 μg/mL has been extensively involved in clinical trials, while numerous studies have concluded that a phenytoin dose of more than 20 μg/mL in certain patients may be optimal[13].

Theoretical equations have been developed to correct total phenytoin serum concentrations when serum albumin levels are abnormal, such as the conventional or revised Sheiner-Tozer Equation (STE), which is used when albumin is ≤3.2 g/dL (32 g/L[15]. Corrected levels can provide physicians with data to understand the established therapeutic range. The first 48 to 72 hours of therapy are crucial to assess a concentration accessible through phenytoin

Table 1: Demographic data of the monitored and unmonitored groups

		Monitored		Unmonitored		Test	P
		Male	**Female**	**Male**	**Female**		
Gender	N	15	5	8	12	5.01	0.025**
	(%)	75%	25%	40%	60%		
Age	Mean	65.6	49.6	53.62	67.1		
	Min-max	35-89	14-67	35-71	49-83		

**, means significant

or when any seizure activity occurs[16]. In one study, 400 adult patients of both sexes were evaluated using the STE regarding their free phenytoin levels. The study revealed a significant difference between the corrected and experimental concentrations of phenytoin (<1.2 mg/L) in 74.4% of hospitalized patients and 21.3% of outpatients [17].

A similar study assessed plasma levels of total and free phenytoin using polarized immunofluorescence and the STE. The assessment of free phenytoin levels using the STE was more precise than immunofluorescence. Consequently, it is a vital tool in daily phenytoin dosage adjustment[18]. Another study suggested using transdermal iontophoresis for therapeutic drug monitoring, where a moderate correlation between the reverse iontophoretic extracted amount of phenytoin and the subdermal concentration was observed. The method showed efficacy in removing the free portion of phenytoin. At a steady state, reverse iontophoresis controlled the modifications in free drug concentrations motivated in the subdermal compartment. The study concluded that the ratio of the amounts extracted was relative to the subdermal concentration ratio, suggesting a non-invasive model for therapeutic drug measurement[16]. Consequently, the assessment of phenytoin to avoid an overdose is critical in susceptible patients because an overdose of phenytoin can be fatal. Overdose symptoms may include twitching eye movements, slurred speech, loss of balance, tremors, muscle stiffness or weakness, nausea, vomiting, light-headedness, fainting, and slow or shallow breathing. Patients should avoid drinking alcohol while taking phenytoin[19].

Hence, the purpose of this study was to prove the significance of monitoring phenytoin to avoid toxicity. The proper timing and understanding of the amounts of phenytoin, its dosing, and other controlling criteria, and the management of adverse effects of phenytoin were also assessed. Therefore, the current study focused on the importance of phenytoin monitoring and encouraging patients and doctors to be careful in its use.

Material and Methods

Study design

Patients were recruited according to inclusion criteria for phenytoin monitoring for this cross-sectional, open-label, randomized observational prospective clinical study. Two groups of epileptic patients (40 patients, Table 1) were randomly chosen for phenytoin monitoring and were subdivided into two groups. The first group was an unmonitored group where two samples of phenytoin serum were collected after one and two months of treatment and checked one month apart. In contrast, the second group was the monitored group, where two samples of phenytoin serum levels were taken with dose adjustment if needed. Another sample was taken after one month. This study was conducted at King Fahad Armed Forces Hospital in Jeddah, Saudi Arabia between November 2022 and March 2023.

Ethical issues and informed consent

All relevant information, like the purpose and methodology of the study, was explained to study participants beforehand, and informed consent was obtained. All procedures of the present study were conducted in compliance with the Helsinki declaration for research on human beings. The study was approved by the local research ethics committee. The study protocol was approved by the Ethical Review Board of King Fahd Armed Forces Hospital – Jeddah, Saudi Arabia (Reference Ethical Number: REC 461).

Table 2: T-test means: Difference between two independent means (two groups)

Analysis:	A priori: Compute the required sample size	
Input:	Tail(s)	One
	Effect size d	1.08
	α error probability	0.05
	Power (1-β error probability)	0.95
	Allocation ratio N2/N1	1
Output:	Noncentrality parameter δ	3.4152599
	Critical t	1.6859545
	Df	38
	Sample size group 1	20
	Sample size group 2	20
	Total sample size	40
	Actual power	0.9562423

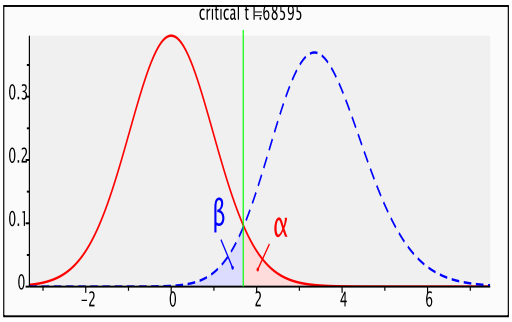

Fig. 2: Critical trail curve.

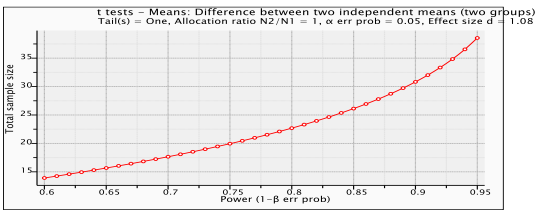

Fig. 3: T-test mean curve

Inclusion and exclusion criteria

The target population included volunteers treated with phenytoin for epilepsy patients in Saudi Arabia. Patients were 18 years old or older and had clinically diagnosed epilepsy. Both male and female patients were included. Patients under the age of 18, pregnant women, patients with chronic comorbidities, patients using phenytoin for another medical disorder were excluded.

Sample size

Sample size calculation was performed using G*Power version 3.1.9.2, Faul et al. (2007), Kiel University, Germany. Copyright (c) 1992-2014. The effect size d was 1.08 using an alpha (α) level of 0.05 and a beta (β) level of 0.05, i.e., power = 95%; the estimated sample size (n) should be 20 samples for each group Table 2 and Fig. 2 and 3.

Sampling and laboratory measurement

History collection was performed with particular emphasis on age and sex. In non-fasting patients, venous blood samples were drawn from an arm vein. Laboratory analyses were done within four hours after the collection of pieces. Whole blood samples were used for:

1. Determination of phenytoin serum level.
2. Determination of kidney function (serum creatinine) with each phenytoin level.
3. Determination of resolution of liver function tests (ALT, AST) with each phenytoin level.

Phenytoin serum levels were measured using the Enzyme-Multiplied Immunoassay Technique (EMIT**)** on an automated chemistry analyzer**.** Blood samples were collected in plain tubes, centrifuged at 3000 rpm for 10 minutes, and the serum was analyzed. The enzymatic activity, inversely proportional to the phenytoin concentration, was measured spectrophotometrically at 340 nm. A standard calibration curve was used for quantification, with the therapeutic range set at 10–20 µg/mL. Quality control samples ensured assay accuracy.

Blood was decalcified using a calcium citrate (3.5%, 109 mM) solution to prevent clotting (9:1 ratio), and plasma was separated by centrifugation using a NuWind centrifuge (NuAire, MN, USA) at 3200 rpm for five minutes for the determination of partial thromboplastin time (PTT) and prothrombin time (PT). Serum was used to determine liver and kidney functions, and blood was centrifuged at 3200 rpm for 15 minutes (NuAire, MN, USA). Concerning serum creatinine, the method was performed colorimetrically using a test reagent kit according to Schirmeister et al.'s process (1964) [1]. Concerning liver function, ALT and AST were performed on patients' serum samples using the Dimension (Siemens, Berlin, Germany), which calculates enzyme activities with a computer. The ALT and AST colorimetric assays were performed using a test reagent kit according to Reitman and Frankel (1957) [2]

Statistical analysis

Using the following statistical tests, all data were collected, calculated, tabulated, and statistically analyzed. A Kolmogorov-Smirnov normality test was done to check the normal distribution of the samples. Descriptive statistics were computed using mean ± standard deviation (SD). Qualitative data were presented as frequencies (n) and percentages (%). A Chi-square test was used to evaluate qualitative data between the categories. A paired and unpaired sample test was used to compare the two groups. P value ≤ 0.05 was considered to be statistically significant. One-way ANOVAs were used to compare the period intervals for each group. Tukey`s post hoc test was performed to evaluate statistical significance among the time intervals.

All statistical analyses were performed using the computer program SPSS software for Windows version 26.0 (Statistical Package for Social Science, Armonk, NY: IBM Corp) at significance levels of .05 (P value <0.05).

Results

Clinical data of monitored and unmonitored groups

Clinical data of the monitored and unmonitored groups are illustrated in Table3. The current dose of most of the patients was 100 mg TID, with 65% and 55% in the monitored and unmonitored groups, respectively. Statistical analysis showed significant differences between current doses between the patients in the monitored (*P*=0.010) and unmonitored groups (*P*=0.018). Concerning the length of treatment with phenytoin, in the monitored group, two cases did not receive treatment, about 50% from one to five years, 35% from five to ten years, and 3% for more than ten years. In contrast, in the unmonitored group, about 15% did not receive treatment, 45% from one to five years, 20% from five to ten years, and 10% for more than ten years. Statistical analysis showed significant differences between current doses between the patients in the monitored group (*P*=0.0088) and insignificant differences in the unmonitored group (*P*=0.9627).

For epilepsy types, the results show 65% primary epilepsy and 35% secondary epilepsy in the monitored group. In contrast, the results show 60% primary epilepsy and 40% secondary epilepsy in the unmonitored group. Statistical analysis showed no significant differences in epilepsy types between the patients in the monitored (*P*=0.1797) and unmonitored groups (*P*=0.3711).

The results concerning clinical status show that in the monitored group, 30% of the patients were bedridden and 70% were mobile. In contrast, in the unmonitored group, 35% were bedridden and 65% were mobile.

Statistical analysis showed no significant differences between epilepsy types between the patients in the monitored (*P*=0.073) and unmonitored groups (*P*=0.1797).

Regarding regular patient visits to the hospital, the results show that in the monitored group, 60% did not make regular visits to the hospital and 40% made regular visits to the hospital. In contrast, in the unmonitored group, 35% did not make regular visits to the hospital and 65% made frequent visits to the hospital. Statistical analysis showed no significant differences between epilepsy types for the patients in the monitored (*P*=0.3711) and unmonitored groups (*P*=0.1797) (Table 3). (Descriptive data for monitored and unmonitored group mentioned in Appendix table A1 and A2).

Distribution of the patients under study by phenytoin level

Patients with phenytoin levels of 40-79 are considered clinically normal, and those with phenytoin levels of less than or more than this level are considered abnormal. The results in Table 4 show that in the monitored group, 75% of patients had levels of less than 40, 20% had 40-79 (average), and 5% had more than 79. In contrast, in the unmonitored group, 35% of patients had levels of less than 40, 50% had 40-79 (average), and 15% had more than 79.

Table 3: Clinical data of the monitored and unmonitored groups

		Monitored		Unmonitored		χ^2	P value
		N	%	N	%		
Current dose	100 mg TID	13	65	11	55	2.49	0.28
	200	3	15	1	5		
	300	4	20	8	40		
	P values	0.010**		0.018**			
Last years	None	-	-	3	15	6.88	0.07
	1-5 years	10	50	4	45		
	5-10 years	7	35	4	20		
	More than 10 years	3	15	3	20		
	P values	0.0088**		0.9627			
Epilepsy types	Primary epilepsy	13	65	12	60	0.11	0.94
	Secondary epilepsy	7	35	8	40		
	P values	0.1797		0.3711			
Clinical status	Bedridden	6	30	7	35	0.113	0.73
	Mobile	14	70	13	65		
	P values	0.073		0.1797			
Regular visits to the hospital	Not regular	12	60	7	35	2.50	0.11
	Regular	8	40	13	65		
	P values	0.3711		0.1797			

Test used: Chi-square at P<0.05

Statistical analysis showed significant differences between phenytoin levels in the patients in the monitored group (*P*<0.0001) and no significant difference in the unmonitored group (*P*=0.1797).

Table 4: Distribution of the patients under study by phenytoin level (n 40-79)

	Monitored (n=20)		Unmonitored (n=20)		Test	P
	N	%	N	%		
Less than 40	15	75	7	35	0.228	0.633
40-79	4	20	10	50		
More than 79	1	5	3	15		
P value	<0.0001**		0.1797			

Test used: Chi-square at P<0.05

Determination of phenytoin serum level

The phenytoin serum levels in the patients in the monitored and unmonitored groups were determined as a baseline after one month and two months (Table5). The results showed no significant difference during the period (baseline, first month and second month) in either group. The high mean phenytoin serum levels decreased by about 7.87% and 3.88% in the first and second months, respectively, compared with the baseline in the monitored group, while these changes were 27.77% and 31.12% increases in the first and second months, respectively, compared with the baseline in the unmonitored group.

Comparison between monitored and unmonitored groups in the same period

Table 6 shows a significant difference between the monitored and unmonitored groups in the first and second months (*P*=0.0246 and *P*=0.04), while there is no significant difference between the groups at the baseline (*P*=0.794).

Table 5: Phenytoin level

		Mean	SD	Median	Range	*%change*	F	P value
Monitored group	Baseline	32.54[a]	12.51	18.55	0.0-112		0.041	0.959
	First month	29.98[a]	16.74	22.64	6.09-106.10	***7.87% (d)***		
	Second month	31.28[a]	14.72	23.43	7.42-117	***3.88% (d)***		
unmonitored group	Baseline	34.96[a]	15.16	29.54	0.78-82.51		0.993	0.377
	First month	44.67[a]	19.51	40.30	10.04-101.19	***27.77% (i)***		
	Second month	45.84[a]	15.55	46.93	9.73-97.56	***31.12% (i)***		

Test used: ANOVA test (F) **: means significant at P<0.05 d: decrease i: increase

Table 6: Phenytoin level

Follow-up	Groups	Mean	SD	T-test	P value
Baseline	Monitored	32.54	12.51	0.269	0.794
	Unmonitored	34.96	15.16		
First month	Monitored	29.98	16.74	6.371	0.0246**
	Unmonitored	44.67	19.51		
Second month	Monitored	31.28	14.72	1.831	0.04*
	Unmonitored	45.84	15.55		

Test used: unpaired sample T-test **: means significant at P<0.05

Determination of kidney function (serum creatinine) at each phenytoin level

The kidney function (serum creatinine) was determined in the patients in monitored and monitored groups after one month and two months. The results showed that there is no significant difference during the period (first month and second month) in the monitored group (P=0.077), while there is a substantial difference during the period in the unmonitored group (P=0.0241) (Table7). The high mean creatinine levels decreased by about 4.83% and 11.48% in the second month compared with the first month in the mounting and unmonitored groups, respectively. Table 8 shows a significant difference between the monitored and unmonitored groups in the first and second months for serum creatinine (P<0.001 and P=0.032).

Discussion

Phenytoin is a regularly prescribed anticonvulsant medicine that can be used to treat both acute and chronic seizures[6]. In the context of prolonged therapy, toxicity might emerge from an intended overdose, dosage variations, pharmacological interactions, or physiological changes[1]. It is vital to monitor drug concentrations in the blood to optimize drug therapy for seizure patients, as the serum concentration is a more reliable measurement of the drug's therapeutic and harmful effects than the provided dosage [20]. The current study aimed to explore the importance of monitored phenytoin to avoid toxicity, the proper timing and dose, and the management of adverse effects.

The current dose of most of the patients was 100 mg TID, with 65% and 55% in the monitored and unmonitored groups, respectively, with no significant association between the two groups[21]. These findings suggested that a loading dose of 10 to 15 mg/kg should be administered slowly intravenously for the treatment of status epilepticus in adults. Maintenance doses of 100 mg orally or intravenously every six to eight hours should be given after the loading dose[22].

Table7: Kidney function

Paired Samples Statistics				Paired mean differences	% change	95% Confidence interval of the difference		T-test	P value
Groups		**Mean**	**SD**			Lower	Upper		
Monitored group	First month	77.84	17.03	3.76	4.83% (d)	0.44	7.96	1.870	0.077
	Second month	74.08	16.62						
Unmonitored group	First month	101.61	22.99	11.66	11.48% (d)	4.21	27.54	8.538	0.0241**
	Second month	89.95	23.19						

Test used: paired sample t-test **: means significant at P<0.05 - d: decrease

Table 8: Comparison of monitored and unmonitored groups for serum creatinine during the same period

Paired Samples Statistics				T-test	P value
Groups		**Mean**	**SD**		
First month	Monitored	77.84	17.03	9.916	<0.001**
	Unmonitored	101.61	22.99		
Second month	Monitored	74.08	16.62	5.826	0.032**
	Unmonitored	89.95	23.19		

Test used: unpaired sample t-test **: means significant at P<0.05

The analysis of blood values is critical since the therapeutic range of phenytoin is so restricted and it has substantial toxicological hazards. As a result, drug level monitoring is recommended during treatment with this medicine [23]. Our results showed no significant difference between levels of serum phenytoin in the monitored and unmonitored groups. The high mean phenytoin serum levels decreased by about 7.87% and 3.88% in the first and second months, respectively, compared with the baseline in the monitored group. Similarly, neither Jannuzzi et al. nor Fröscher et al. identified a significant difference in mean phenytoin serum concentrations between monitored and unmonitored groups[24, 25]. In Woo et al.'s study, all randomized participants in both groups had been seizure-free for three months and had subtherapeutic levels at study enrolment[26]. At the end of the two-year research, there was no significant difference between the control group, which was managed clinically without levels, and the monitored group, whose dose was modified to ensure levels were increased to the therapeutic range. In addition, after six months, Sivasankari et al. found a difference in mean serum phenytoin concentration between the monitored and unmonitored groups (P<0.001), with the monitored group increasing by 73.33% and the unmonitored group increasing by 28.29%[27]. Two articles reported that a significant rise in medication concentration was related to an improvement in seizure control in the monitored group[28, 29].

The current study showed that the incidence of phenytoin toxicity was not high (5% in the monitored group and 15% in the unmonitored group). The reason could be that not all patients have chronic liver disease, which is not common in Saudi Arabia, or the small sample of the study. According to Woo et al. (48), there was no significant difference in AED toxicity between the monitored and unmonitored groups. However, the AED level group had increased drug toxicity, with 35% experiencing systemic toxicity compared to 30.8% in the unmonitored group. Furthermore, therapeutic drug monitoring (TDM) showed no significant difference in adverse effects in two other investigations[24, 30]. McKee et al. found a significant difference in drug-related toxicity of 56% for unmonitored patients versus 25% for monitored patients[29].

Acute kidney injury was thought to have been caused by medication as a result of uncontrolled phenytoin use, which has been linked to nephrotoxicity[31]. The current results confirmed these studies: This study reported a significant increase in the creatinine level in the first and second months among the unmonitored group. This means that the unmonitored group was at higher risk of kidney injury. As a result, if the creatinine level exceeds the normal range, the medicine should be discontinued immediately, and corticosteroid therapy should be initiated as soon as possible [32, 33]

This research aimed to improve monitoring information to reduce the occurrence of toxicity by determining the initial effective dosage, monitoring plasma levels, and understanding that the risks of drug intake are severe and difficult to predict. This study is critical because it attempts to shed light on assessing and evaluating awareness. Our study had several strengths: The patients we worked with were of different age groups. The study was conducted for the first time on Saudi patients. Not many Saudis understand the significance of monitoring phenytoin to prevent toxicity However, further study needs large numbers of volunteer patients, and the cost of collecting the sample and laboratory results is high. Our recommendations include avoiding the use of phenytoin among patients who do not have access to the hospital, such as bedridden patients, encouraging physicians to observe their patients on phenytoin closely, and teaching caregivers and patients about the signs and symptoms of phenytoin toxicity.

Conclusion

This study reports lower phenytoin toxicity among a monitored group (5%) than an unmonitored group (15%) of Saudi epileptic patients, which confirmed most previous studies. The serum phenytoin level was significantly higher in the first and second months of follow-up among unmonitored patients. The baseline kidney functions and serum creatinine levels in the first and second months were higher for the unmonitored group, which reflects the higher risk of kidney injury than was expected in the monitored group. These results show the importance of monitoring the drug phenytoin to avoid its toxicity and side effect.

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Financial Disclosure

There was no specific funding source to be mentioned.

Conflict of Interest

The authors declare that they have no conflict of interest.

Institutional Review Board Statement

Ethical considerations provided by WHO regarding human subjects selected for experiments were fulfilled (Approved No REC 461).

Informed Consent Statement

Written informed consent has been obtained from the patient(s) to publish this paper

Author Contributions

NA and SA designed the study. GA, HY, MA have performed the study. AF and YA performed the validation of the study. MA and HY assisted the formal analysis. GA, MA, WA, and HY have assisted and supported in sample collection and subsequent analysis with statistics. NA, SSA and AA supervised and investigated the study. AF, and YA supported the resources. GA, HY, MA, AF, YH and WA assisted in writing—original draft preparation. NA, SA, SSA and AA have carefully supervised this manuscript preparation and writing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviation List:

AEDs: Antiepileptic drugs
AEDs: Anti-epileptic drugs
ALT: Alanine aminotransferase
ANOVA: Analysis of Variance
ASD: Antiseizure Drugs
AST: Aspartate aminotransferase
NTI: Narrow therapeutic index
REC: Reference Ethical Number
SD: Standard deviation
STE: Sheiner-Tozer Equation
TDM: Therapeutic drug monitoring
TID: Three times daily

Appendix A

TableA1: Descriptive data for the monitored group

	Sex	Age	Common factors	Years of use	ASD	Current dose	Last years	Epilepsy subtypes
1	M	84	cholesterol – diabetes – hypertension	2002	alfuzosin – glimepiride – fosinopril	100	2016	primary epilepsy
2	M	52	cholesterol – diabetes	2002	allopurinol – gabapentin	100	0	primary epilepsy
3	M	68	cholesterol – cardio – diabetes	2016	glimepiride	100	0	primary epilepsy
4	M	64	cholesterol – cardio – diabetes	2004	sodium valproate	300	2011	primary epilepsy
5	M	64	cardio - cholesterol	2019	allopurinol – carbamazepine	100	2020	structural epilepsy
6	M	80	hypertension – BA	2017	amantadine – paroxetine – levetiracetam	300	2019	primary epilepsy
7	M	35	thyroid	2007	carbamazepine – escitalopram – levetiracetam – thyroxine sodium	300	2020	primary epilepsy
8	F	67	cholesterol – cardio	2006	carbamazepine	200	2019	primary epilepsy
9	M	48	-	2007	-	200	2021	primary epilepsy
10	M	89	hypertension – cardio – cholesterol	2005	levetiracetam	100	2020	structural epilepsy
11	M	44	cardio	2017	carbamazepine – escitalopram – topiramate	100	0	primary epilepsy
12	F	54	-	2010	-	100	2013	primary epilepsy
13	M	68	hypertension – KD	2020	allopurinol – levetiracetam	100	0	structural epilepsy
14	F	65	hypertension – diabetes – cholesterol	2018	levetiracetam – escitalopram – carbamazepine	200	2021	structural epilepsy
15	F	48	diabetes	2005	amitriptyline – carbamazepine – levetiracetam	300	2006	structural epilepsy
16	M	71	cholesterol – diabetes – cardio	2000	levetiracetam – fosinopril	100	2020	primary epilepsy

17	F	14	-	2017	baclofen	100	2017	secondary epilepsy
18	M	71	cardio – cholesterol – diabetes	2019	escitalopram – fosinopril – levetiracetam – quetiapine	100	2021	structural epilepsy
19	M	81	hypertension – cardio – cholesterol	2017	rivastigmine	100	0	primary epilepsy
20	M	65	cholesterol – diabetes – hypertension	2011	insulin – metformin	100	2013	structural epilepsy

Table A2: Descriptive data for the unmonitored group

P.N	Sex	Age	Common factors	Years of use	ASD	Current dose	Last year	Primary
1	M	41	none	2011	none	300	2011	structural epilepsy (post-tumor excision)
2	F	72	dysuria – diabetes	2000	gabapentin – topiramate – levetiracetam	100	2018	primary
3	F	59	hypertension	2014	topiramate	100/2t-d	2019	primary
4	M	64	hypertension	2000	levetiracetam – topiramate	100/2t-d	2014	primary
5	M	60	diabetes	2000	none	300	2004	structural epilepsy (post-stroke)
6	M	44	diabetes, hypertension	2019	none	100	none	structural epilepsy (metastasis)
7	M	61	diabetes – renal cell carcinoma – brain metastasis	2019	levetiracetam	100/2t-d	none	primary
8	F	68	hypertension	2000	none	100/3t-d	2018	structural epilepsy post-stroke
9	F	49	diabetes	2013	none	100/3t-d	2014	primary
10	F	60	ischemic heart disease	2000	none	300	2018	primary
11	M	53	carvedilol – heart failure	2002	levetiracetam	300	2014	structural (post-stroke)
12	F	70	hypertension	2003	none	200	2021	secondary seizure (anoxic brain injury)
13	M	35	cerebral palsy	2005	none	100	2006	primary
14	F	83	cardio - hypertension - diabetes - kidney	2013	lamotrigine – sodium valproate	100	2021	primary
15	M	71	cardio - diabetic	2002	gabapentin	300	2010	primary
16	F	54	obesity	2012	gabapentin	100	none	structural post-stroke
17	F	75	stroke	2014	carbamazepine	300	2018	structural post shunt
18	F	53	thyroxin	2000	none	300	2019	primary epilepsy
19	F	83	hypertension – cardio – diabetes – ESRD	2016	none	300	2016	primary epilepsy
20	F	79	hypertension – cardio – diabetes – thyroid	2019	none	100	2020	primary

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