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Research article

Monitoring Serum Concentrations of Phenytoin in Epileptic Patients

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Abstract

Phenytoin has complex pharmacokinetic profile with wide inter-individual variation. Due to its wide fluctuations, dosage must be carefully monitored which otherwise can lead to adverse reactions or loss of therapeutic efficacy. This study aimed at monitoring serum concentrations of phenytoin and to determine the therapeutic range in which there is seizure control and to monitor the adverse drug reactions caused due to phenytoin. Blood samples were collected from patients after steady-state concentration of phenytoin was reached. Serum phenytoin concentrations were measured using chemiluminescent enzyme immunoassay method (CLIA). From 93 patients, a total of 114 samples were collected among whom male patients were 41 (44.1%). Wide variability in serum concentrations of phenytoin was observed which ranged from 2.4 – 30 µg/ml. Phenytoin concentrations were subjected for analysis with various independent variables such as age, gender, weight, co-administered drugs, alcohol and it was observed that there is no effect of these variables on the serum concentrations of phenytoin. There were no major toxicities due to phenytoin except giddiness, nystagmus, headache, mild gingival hyperplasia and mild thrombophlebitis. In conclusion, dosage adjustment of phenytoin was not required since therapeutic benefit was observed in all the patients even at concentration 2.4 µg/ml, without major toxicities.

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Keywords

Phenytoin, CLIA, Serum Concentrations, Co-medication, Alcohol

INTRODUCTION

About 1% of the population worldwide[1] and 50 – 100 lakh in whole of India[2] are estimated to have epilepsy, and antiepileptic drugs (AEDs) are often used for lifelong treatment. Phenytoin (PHT) is an anticonvulsant drug introduced by Merritt and Putnam in 1938 which remains as one of the most widely prescribed drugs for the treatment of epilepsy.[3] The usual therapeutic range phenytoin is considered to be 10 – 20 µg/ml. Phenytoin exhibits non-linear complex pharmacokinetics, has a narrow therapeutic range, is highly bound to plasma proteins (almost 90%), follows saturable metabolism. Though phenytoin is almost metabolized, it has a very low metabolic clearance (0.017 L/hr/kg), elimination follows non-linear Michaelis-Menten pharmacokinetics and it is mainly eliminated through oxidative hepatic metabolism by isoenzymes CYP2C9 and CYP2C19 of the cytochrome P450 system.[4] Due to its marked enzyme inducing property, phenytoin may cause clinically relevant drug-drug interactions. The therapeutic range of free concentration of phenytoin is about 10% of that of the total phenytoin concentration.[5] Stable phenytoin levels at steady-state are obtained in most patients in seven to ten days after initiation of oral therapy with recommended doses of 300mg/day.[6] Due to its wide fluctuations in their concentration values, dosage adjustments must be carefully monitored where small changes in the dosage can lead to either toxic effects causing adverse reactions or loss of therapeutic efficacy. Because of its narrow therapeutic range and saturation kinetics, therapeutic drug monitoring of phenytoin is justified to ensure patient safety and efficacy. Monitoring phenytoin concentration can aid in rationally adjusting dosages and preventing life threatening toxicity.[7] Hence, a study was conducted to

a) Monitor serum phenytoin levels to determine the therapeutic range in which there is seizure control.

b) Suggest dosage adjustment to the clinicians whenever the phenytoin concentrations are out of therapeutic range and also if seizures are not controlled.

c) Monitor the adverse drug reactions (if any) caused due to the administration of phenytoin.

METHODOLOGY

Phenytoin was chosen as the model drug upon the request of the clinicians of St. Martha's Hospital. Ethical committee clearance was obtained from the Institutional Review Board of St. Martha's Hospital, Bangalore. This prospective intervention study was conducted in in-patient medicine department of a tertiary care teaching hospital. Patients of both genders, receiving phenytoin as slow IV injection at a rate not exceeding 50mg/minute in adults. In neonates and children, the drug administered at a rate not exceeding 1–3mg/kg/minute and/or oral administrations of 300 mg/day were included in the study. Pregnant and lactating mothers were excluded. Consent was obtained from all the patients before enrolling. Data was

collected from the case sheets and by interviewing the patients and blood samples were collected only after the patient attained the steady-state concentration of phenytoin. Serum concentrations were measured using chemiluminescent enzyme immunoassay (CLIA) method. Before analyzing the serum concentrations of phenytoin, the instrument IMMULITE was calibrated using the control sample available in the kit and the level of detection of phenytoin concentration was adjusted using low and high adjustors respectively. After calibration, the instrument slope was found to be 0.98 – 1.47 and the mean CV of low adjustor was found to be 1.401% and with the high adjustor the mean CV was 1.753%.

RESULTS AND DISCUSSION

The study included 114 serum samples of phenytoin from 93 patients, among whom male patients were 41 (44.1%). Gender predomination was commonly observed in previous studies.[8,9] As per the methodology, both pediatrics and adult patients were included in the study. Age group of the patients ranged from <10 years to >80 years. The mean age of the patients was found to be 46.29±21.19 years. Majority of our patients [53 (57%)] were between the age of 20–60 years, followed by [26 (28%)] patients >60 years and the remaining [14(15%)] were below the age of 20 years (Table 1). Studies have reported that V_{max} decreases with age, but there is no age relationship for K_m. As a result of these changes, the 60-to-79 year old group would require on the average, 21% less phenytoin per day than the 20- to 39-year-olds to maintain a steady-state concentration of 15 microgram/ml.[10] Literature supports to have more adult epileptic patients enrolled in previously conducted studies.[11]

Data of patient's weight was collected and it was observed that most of the patients 31 (33.3%) had weight between 61-70 kgs followed by 25 (26.9%) patients between 71-80 kgs. The mean weight of the patients was found to be 62.8±13 kgs. It was also observed that the liver enzymes in [30 (53.8%)] patients were normal, followed by slightly increased in [8 (8.6%)] and very high in [5 (5.4%)] patients. Liver function test was not done in the remaining [50(53.8%)] patients. The reasons for carrying out LFT includes patients could not afford the test cost, treating physician's decision (Table 2).

Alcohol consumption was checked in the study population and found that 71 (76.3%) patients did not consume alcohol and 22 (23.7%) had varied levels of alcohol consumption (Fig.1). Out of these 22 patients, 11 patients serum phenytoin concentration was below 10 µg/ml followed by 7 patients with phenytoin concentration in therapeutic range. Only 4 patients had their phenytoin concentrations above 20 µg/ml. Studies have stated that increased phenytoin clearance in alcoholics is due to increased metabolic rate of the drug secondary to enzyme induction by alcohol.[12]

Data of concomitant medication was collected to check for the possible effect of the co-medication on the serum concentration of phenytoin. Co-medication considered of having

Table 1: Age distribution of patients studied

Age in years	No. of patients	Percentage
<10	3	3.2
11-20	11	11.8
21-30	12	12.9
31-40	12	12.9
41-50	11	11.8
51-60	18	19.4
61-70	12	12.9
71-80	12	12.9
>80	2	2.2
Total	**93**	**100.0**

Mean ± SD: 46.29±21.19

Table 2: Liver function test

Liver function test	No. of patients	Percentage
LFT is not done	50	53.8
LFT is normal	30	32.3
LFT is moderately above normal	8	8.6
LFT Values are very high	5	5.4
Total	**93**	**100.0**

an effect included ACE inhibitors, diuretics, valproate, phenobarbital, fluroquinolones, anticoagulants, aspirin, antacids, carbamazepine, levetiracetam any other antiepileptic drugs. According to the data, most of the patients [57 (61.3%) patients] received antacids out of whom only 1 patient had phenytoin concentration of 29.5 µg/ml remaining 56 patients had concentration values less than 25 µg/ml. Studies has shown that antacids given in therapeutic doses will not affect the phenytoin concentrations.[13]

Diuretics were prescribed to [44(47.31%)] patients and 1 patient each received prescription of phenobaritone, carbamazepine.

Table 3: Distribution of data according to the serum concentration range of Phenytoin

CONCENTRATION	GEN	LFT	PREG →	ACEI	DIU	VAL	PHEN	FQ	WARF	ANTICOAG	ASP	ANTCD	CARB	LAMO	LEVET	OAEDS	ALCOH
SUB-THERAPEUTIC (<10 µg/ml) - 51	F, 23 M, 28	A, 29 B, 00 C, 14 D, 05 E, 03	NO	50	21	51	51	49	51	46	46	34	51	51	49	38	40
			YES	1	30	0	0	2	0	5	5	17	0	0	2	13	11
THERAPEUTIC (10-20 µg/ml) - 30	F, 15 M, 15	A, 15 B, 00 C, 10 D, 03 E, 02	NO	27	13	29	30	29	30	25	24	8	29	30	22	17	23
			YES	3	17	1	0	1	0	5	6	22	1	0	8	13	7
SUPRA-THERAPEUTIC (>20 µg/ml) - 12	F, 3 M, 9	A, 06 B, 00 C, 06 D, 00 E, 00	NO	12	5	10	11	12	12	10	10	4	12	12	12	10	8
			YES	0	7	2	1	0	0	2	2	8	0	0	0	2	4
TOTAL NO.OF PATIENTS	93	93		93	93	93	93	93	93	93	93	93	93	93	93	93	93

GEN=Gender; F→ female; M→male; LFT→Liver function Test; A = Not done; B = Done; C = Normal; D= moderately high; E = high; ACEI→Angiotension Converting Enzyme; DIU→Diuretics; VAL→ Valproate; PHEN→Phenobarbitone; FQ→Fluroquinolones; WARF→Warfarin; ANTICOAG→Anticoagulants; ASP→Aspirin; ANTCD→Antacids; CARB→Carbamazepine; LAMO→Lamotrigene; LEVETIRA→ Levetiracetam; OAEDS→ Other Anti-Epileptic Drugss; ALCOH→Alcohol.

Patient who was prescribed with phenobarbitone also had diuretic prescribed in the treatment regimen and the serum phenytoin level in this patients was >40 µg/ml. The increased in the phenytoin concentration beyond 40 µg/ml can be related to the analytical error or can be due to co-administration of phenytoin and phenobarbitone, but there were no adverse drug reactions observed in the patient. There are no such studies to our knowledge which showed effect of diuretics on phenytoin. From 93 patients, a total of 114 samples were collected at different time points. Wide variability in serum concentrations of phenytoin was observed in our patients that ranged from 2.4 – 30 µg/ml. As per the literature, patient age, weight, gender, compliance was assumed to be the reasons for variability.[14] In our study we did not find patients with high/toxic therapeutic concentrations (>30 µg/ml) except in one patient (>40 µg/ml). Our study results are similar to the study conducted by Kishore P et al, where it was reported that the lower concentration of phenytoin was found to be 3.9 µg/ml[15], and in another study conducted by Elizabeth M et al in 56 patients, the total phenytoin concentrations ranged between 0.3 – 29.4 µg/ml.[16] There are other such studies which draw attention on having wide variations in serum concentrations of phenytoin.[6,17-19] In our study, 51 patients were found to have sub-therapeutic levels of phenytoin [<10 µg/ml) followed by 30 patients in therapeutic range (10-20 µg/ml) and only 12 patients exhibited concentrations >20 µg/ml. The distribution of the complete data according to the serum phenytoin concentration is shown in Table 3. Despite sub-therapeutic levels of phenytoin, all the patients in our study showed seizure control. This may be due to the presence of optimum free phenytoin concentration despite the low total serum concentrations. According to Kishore P et al, 75% of patients with sub-therapeutic levels of phenytoin exhibited good seizure control.[15] Turnbell et al reported that serum phenytoin levels were infinitely variable, they also had patients with no seizures at low therapeutic concentrations[20], but partial control in seizure activity was seen in patients with sub-therapeutic levels in the study conducted by Mawer GE et al.[21]

We also determined the effect of concomitant medication like anticoagulants (enoxaparin, clopidogrel), anti- inflammatory agents (aspirin), antacids (pantaprazole) and calcium supplementation on the serum phenytoin levels. As per the literature, omeprazole, clopidogrel, aspirin will reduced the clearance of phenytoin leading to increase the serum concentrations of phenytoin and concurrent administration of antacids, calcium may decrease the bioavailability of phenytoin.[22,23]

Serum phenytoin concentrations were subjected for analysis with various independent variables like fluroquinolones, anticoagulants, aspirin, antacid, levetiracetam, OAEDs, alcohol and it was observed that there was no effect of these variables on the serum concentrations of phenytoin. In our study we found that co-medication has no effect on serum phenytoin levels in our population (Tables 4).

Table 4: Concentration levels in µg/ml according to different independent variables

Concentration levels in µg/ml according to time	Min-Max	Mean ± SD	P value
Angiotensin converting enzyme inhibitor			
• Not given	0.00-30.00	10.15±7.27	0.218
• Given	9.80-18.60	14.70±4.58	
Diuretics			
• No	2.40-30.00	9.56±7.79	0.263
• Yes	0.00-24.70	11.08±6.59	
Valproate			
• No	0.00-30.00	10.02±7.06	0.010**
• Yes	13.20-24.70	20.87±6.64	
Phenobarbital			
• No	2.40-30.00	10.28±7.11	0.711
• Yes	0.00-24.40	12.2±17.25	
Fluroquinolones			
• No	0.00-30.00	10.34±7.36	0.844
• Yes	8.05-11.30	9.61±1.33	
Anticoagulants			
• No	0.00-30.00	10.08±7.20	0.355
• Yes	2.40-24.70	12.07±7.55	
Aspirin			
• No	0.00-30.00	10.03±7.36	0.303
• Yes	2.82-24.70	12.04±6.36	
Antacid			
• No	0.00-30.00	8.70±7.28	0.070+
• Yes	2.40-29.90	11.25±7.09	
Levetiracetam			
• No	0.00-30.00	10.22±7.56	0.762
• Yes	2.40-17.10	10.80±5.10	
Other anti-epileptic drugs			
• No	0.00-30.00	10.15±7.43	0.704
• Yes	2.40-24.70	10.73±6.78	
Alcohol			
• No	0.00-30.00	10.08±6.60	0.556
• Yes	2.40-29.90	11.01±9.00	

Throughout the study period, we did not notice any major toxicities due to phenytoin except giddiness, nystagmus, headache, mild gingival hyperplasia and mild thrombophlebitis. One patient had a severe skin eruption that was treated symptomatically but we could not relate the ADR to drug level as the serum phenytoin concentration was within the therapeutic range. As per the literature, phenytoin has high incidence of causing skin eruptions[24] but in our study, concentration levels and side effects did not show any co-relation. Supporting this is a study conducted by Hussein A et al where they found no relationship between serum levels of AEDs and their side effects.[24] Causality assessment using Naranjo Algorithm was carried out to assess the causality between the reactions and the drug and it showed that the reactions were probably due to phenytoin including the patient with severe reaction (Table 5). Our results are similar to the study conducted by Roopa et.al who reported that causality was probable in 65.62% of cases.[25]

Table 5: Causality assessment of Adverse Drug Reactions in study population

Adverse drug reaction	No. of patients	%
Nil	92	98.9
Mild	0	0.0
Moderate	0	0.0
Severe	1	1.1
Total	**93**	**100.0**

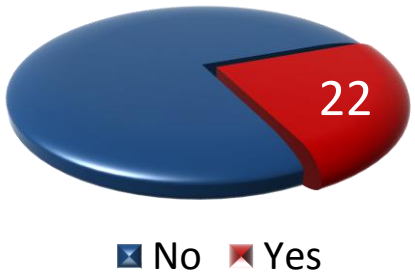

Fig.1: Evaluation of Alcohol consumption in study patients

In our study, dosage adjustment of phenytoin was not encouraged since therapeutic benefit (seizure control) was observed in all the patients even at concentration 2.4 µg/ml, without major toxicities.

LIMITATIONS

We could not analyze following due to the lack of financial support and certain instruments.

1. Free phenytoin concentration levels
2. Protein Binding

SCOPE OF THE STUDY

From our study results, future studies can be planned to determine whether phenytoin therapeutic range need to be revised for Indian epileptic patients or not.

CONCLUSION

Knowledge on concentration and necessity in monitoring of phenytoin is important for better management of epilepsy in patients with recurrent seizures. From our study the following conclusions can be made:

- Wide fluctuations in phenytoin serum concentration levels were observed.
- Many patients were found to be sub-therapeutic i.e. < 10 µg/ml but seizure control was seen in all patients.
- No major ADRs were observed in our study excluding one patient who had severe skin eruption in early stages of the treatment, which was symptomatically treated.
- Dosage adjustment of phenytoin was not done as there was seizure control despite low concentrations.

Finally, we conclude that recommending change in phenytoin dosing should not only rely on concentration ranges but patients' clinical response also should be considered.

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REFERENCES

1. Johannessen LC, Johannessen IS. Safety aspects of antiepileptic drugs-focus on pharmacovigilance. Pharmacoepidemiology and drug safety 2012;21:11-20.
2. Indian Epilepsy Centre [Online]; Available at: http://www.indianepilepsycentre.com/faqs-incidence.html. Accessed on 15-07-2015.
3. Lascelles PT, Kocen RS, Reynolds EH. The distribution of plasma phenytoin levels in epileptic patients. J Neurol Neurosurg Psychiat 1970; 33:501-505.
4. Aliwarga T, Cloyd JC, Goel V, Brundage RC, Marino SE, Leppik IE, et.al. Excretion of the principal urinary metabolites of phenytoin and absolute oral bioavailability determined by use of a stable isotope in patients with epilepsy. Ther Drug Moni 2011; 33(1):56-63.
5. Man Hong-Ji, Chul Choi Y, Joo Kim-W. Differences between the measured and calculated free serum phenytoin concentrations in epileptic patients. Younsei Med J 2009; 50(4):517-520.
6. Pillai LV, Vaidya N, Khade AD, Hussainy S. Variability of serum phenytoin in critically ill injured patients in intensive care unit. Indian J Crit Care Med 2008;12(1):24-27.
7. Winckelmann SL, Spriet I, Willems L. Therapeutic drug monitoring of phenytoin in critically ill patients. Pharmacotherapy2008;28(11);1391–1400.
8. Peterson GM, Mclean S, Aldous S, Witt RJV, Millingen KS. Plasma protein binding of phenytoin in 100 epileptic patients. Br J Clin Pharmac1982; 14:298-300.

9. Hoan LB, Michael EB, Michael SR. Interpatient and intrapatient variability in phenytoin protein binding. Thera Drug Monit: 2002; 24(3):379-385.
10. Bauer LA, Blouin RA. Age and phenytoin kinetics in adult epileptics. Clin Pharmacol Ther. 1982; 31(3):301-304.
11. Fukuoka N, Uno J, Tsukamoto T, Houchi H, Kimura M, Morita S. Dose adjustment of phenytoin for co-medication in Japanese patients With epilepsy. Ther Drug Monit 2009; 31:57-62.
12. Sandor P, Sellers EM, Dumbrell RN, Khouw V. Effect of short- and long-term alcohol use on phenytoin kinetics in chronic alcoholics. Clin Pharmacol & Thera 1982; 30(3):390-397.
13. O`Brien LS, Orme MLE, Breckenridge AM. Failure of antacids to alter the pharmacokinetics of phenytoin. Br J Clin Pharmac 1978;6:176-177.
14. Houghton GW, Richens A, Leighton M. Effect of age, height, weight and sex on serum phenytoin concentration in epileptic patients. Br J Clin Pharmac 1975; 2:251-256.
15. Kishore P, Manohar K, Umesh T, Sagar JV, Krishna DR. Variability of serum phenytoin concentration in Indian epileptic patient population. Indian journal of pharmaceutical sciences 2004:802-805.
16. Rimmer EM, Buss DC, Routledge PA, Richens A. Should we routinely measure free plasma phenytoin concentration?. Br J clin Pharmac 1984; 17:99-102.
17. Garg SK, Gupta MC, Handu SS, Bhargava VK. Therapeutic drug monitoring of antiepileptic drugs-a preliminary experience. Indian Journal of Pharmacology 2000; 32:28-30.
18. Mooradian AD, Hernandez L, Tamai IC, Marshall C. Variability of serum phenytoin concentrations in nursing home patients. Arch Intern Med. 1989:149(4):890-892.
19. Birnbaum A, Hardie NA, Leppik IE, Conway JM, Bowers S, Lackner ET. Variability of total phenytoin serum concentrations within elderly nursing home residents. Lippincott Williams and Wilkins 2003; 2:534-559.
20. Turnbull DM, Rawlins MD, Weightman D, Chadwick DW. Therapeutic serum concentration of phenytoin: the influence of seizure type. Journal of Neurology Neurosurgery and Psychiatry 1984; 47:231-234.
21. Mawer GE, Mullen PW, Rodgers M, Robins AJ, Lucas SB. Phenytoin dose adjustment in epileptic patients. Br J Clin Pharmac 1974; 1:163-168.
22. Pfizer New Zealand. Data sheet dilantin phenytoin. 2013 may. 1-13.
23. Meyer A. Interaction of proton pump inhibitors with cytochromes P450:Consequences for Drug Interactions. Yale Journal of bio and med 1996; 203-209.
24. Hussein A, Abdulgalil A, Omer F, Eltoum H, Hamad A, El-Adil O. Correlation between Serum Level of Antiepileptic Drugs and their Side Effects. Oman Medical Journal 2010; 25(1):17-21.

25. Narayan SRB, Sharma SS, Rodrigues GRK, Kulkarni, C. Pattern of adverse drug reactions to anti-epileptic drugs: a cross-sectional one-year survey at a tertiary care hospital. Pharmacoepidem. Drug Safe 2008; 17(8):807–812.

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.