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Original Article

Translating Phenytoin Therapeutic Drug Monitoring for Potential Utilities to Pharmacovigilance: Capacity Raking an Established Tertiary Care Service

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Abstract

Introduction: Properly applied therapeutic drug monitoring (TDM) is a proven method of reducing adverse drug events and hence health-care costs. It involves laboratory measurement of a chemical parameter of difficult to manage therapeutic drugs at the designated interval for optimization of therapy with these drugs.

Objectives: The objectives of the study were optimization of Pharmacodynamic responses by pharmacokinetic based adjustments in drug use taking phenytoin as a probe and investigation of the quality of requisitions made for TDM

Materials and Methods: This was a hospital-based prospective study done in cases of idiopathic epilepsy (n = 90). Pd analysis was performed by evaluating the clinical response to phenytoin therapy, adverse drug reaction monitoring, and causality categorization using the WHO-UMC causality categories and CDSCO criteria for the seriousness of adverse events. Phenytoin PK analysis was done by enzyme immunoassay technique. An audit of 135 requisitions for the quality of the information received was done by devising a scoring scale.

Results: Pd analysis of 90 patients revealed that 79% of patients responded positively to phenytoin after treatment optimization or could be tapered off phenytoin successfully after achieving seizure control and remained seizure free for the period of follow-up. A total of 8% of patients needed a second antiepileptic drug in addition to phenytoin and 13% of patients were discontinued from phenytoin either because of adverse effects or because phenytoin did not modify seizure activity in these patients. Gum hypertrophy was the most common adverse effect seen in this patient population. PK data for 87 patients revealed that mean serum phenytoin trough (C_0) concentration was 12.105 ± 0.433 μg/ml, mean serum phenytoin peak (C_4) concentration was 16.895 ± 0.571 μg/ml, and mean area under plasma concentration-time curve was 57.99 ± 1.76 μg/ml/h. Audit of 135 TDM requisitions revealed that 40% requisitions were graded as unacceptable, 25% requisitions were of poor quality, 26% requisitions were incomplete, 9% requisitions were satisfactory, while none of the requisitions was complete.

Conclusion: TDM remains a largely underutilized tertiary care resource and best practice guidelines and professional standards of practice need to be adopted for optimum utilization of this resource.

Key words: Pharmacodynamics, Pharmacokinetics, Pharmacovigilance, Phenytoin, Therapeutic drug monitoring

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INTRODUCTION

Monitoring is the essence of therapeutics. One may measure the desired therapeutic and undesired adverse outcomes clinically. Alternatively, a biomarker may be measured.[1] Drug concentration measurement is needed when other measures of monitoring fail. Monitoring has more recently

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extended to dosage adjustments on the basis of DNA sequencing of drug metabolizing enzyme genes.[2] Although pharmacokinetic (PK)-based individualized therapy has been in use since 1970's, evidence is mounting that the current use is still suboptimal.[3-5] Continuously escalating health-care costs and increasing consumer awareness have drawn attention toward laboratory test utilization as these have a significant share in health-care costs and therapeutic drug monitoring (TDM) has no exception in this regard.[6,7]

The literature is scanty with regard to the quality of requests made for TDM although key inputs from requesting physicians are vital for meaningful interpretation of drug concentration measurements. While the quality of requests made for serum digoxin concentration has been reported to be generally unsatisfactory,[8] no report is available regarding the quality of requests for antiepileptic drugs (AEDs) and non-AEDs other than digoxin.

With older opportunities existent for evaluating the definitive role of TDM for drugs whose patent lives have expired (e.g. aminoglycosides and digoxin) and opportunities continuing to arise with newer agents (such as mycophenolic acid and newer AEDs) that are likely to require TDM,[9-11] strategiesfor quality improvement in TDM are needed. Further, the explosion in biotechnology, ease of genotyping, and intensive pharmacovigilance[11] are taking therapeutic monitoring to newer horizons, and there is a need for translating such practices for clinical benefits. We investigated the PK and pharmacodynamic (Pd) (therapeutic and/or adverse) responses to phenytoin in a tertiary care setting in India.[7] This study looks at existing deficiencies in the translation of TDM recommendations to bedside using phenytoin as a probe drug and is the first study to investigate the quality of requisitions made for TDM.

MATERIALS AND METHODS

This was a hospital-based prospective study conducted in the Department of Clinical Pharmacology at Sher-i-Kashmir Institute of Medical Sciences and Government Medical College, Srinagar, after obtaining the Ethical Approval. The study group constituted of cases of cryptogenic or idiopathic epilepsy ($n = 90$) who participated entirely on voluntary basis. Pd analysis was perforemed by evaluating clinical response to phenytoin therapy, adverse drug reaction (ADR) monitoring, and subsequent causality categorization. All ADRs were recorded and reported to National Coordination Centre, Indian Pharmacopia Commission (NCC-IPC) vide VigFlow. Causality assessment was done using WHO-UMC causality categories, for ADRs with objective evidence either in the form of clinical signs on examination and/or lab investigation like nerve conduction velocity, serum phenytoin concentration. The same ADRs were subjected to categorization as serious or otherwise as per the CDSCO criteria for serious adverse events.

Phenytoin PK analysis was done by a validated immunoassay technique using Syva enzyme immunoassay (EMIT) 2000 phenytoin assay kit for the estimation of serum phenytoin trough, peak, or random levels as needed. The sensitivity level of the EMIT phenytoin assay is 0.5 μg/ml with a confidence level of 95%.

An audit of 174 requisitions for the quality of the information received was done exclusive of PK and Pd evaluation. Of the 174 requisitions, 39 requisitions were excluded from the audit on the basis of considering these situations as part of advocacy and sensitization of the prescribers on a rational approach to the TDM under the Information, Education, and communication activity of the Department of Clinical Pharmacology. The scoring scale was devised for quality assessment of remaining 135 requisitions with patient details written by the treating doctors, on the basis of their own pre-awareness level of knowledge and understanding of TDM, which are required for meaningful interpretation of drug concentration measurements [Table 1].

The software package SPSS version 22 was used for statistical analysis. Shapiro–Wilk test was used to check the sample for normal distribution of phenytoin PK parameters. The area under concentration-time curve (AUC_{0-4}) was derived numerically by linear trapezoidal method from peak and trough phenytoin concentrations using non-compartmental analysis. Results are presented as mean ± standard deviation, median, or percentage as applicable. A $P < 0.05$ was taken as statistically significant.

RESULTS

An analysis of clinical response to phenytoin revealed that 79% of patients responded positively to phenytoin after treatment optimization or could be tapered off phenytoin successfully after achieving seizure control and remained seizure free for the period of follow-up. 8% of patients

Table 1: Quality assessment of requisitions received for therapeutic drug monitoring

Available detail	Score	Quality
Name, MRD No.	1	Unacceptable
I + Diagnosis	2	Poor
II + Dose of drug to be monitored	3	Incomplete
III + Indication for drug level monitoring	4	Satisfactory
IV + Timing of sampling relative to last dose	5	Desirable

could not achieve satisfactory therapeutic control with phenytoin alone and needed a second AED in addition to phenytoin. 13% of patients were discontinued from phenytoin either because of adverse effects or because phenytoin did not modify seizure activity in these patients. Figure 1 shows the distribution of patients on the basis of phenytoin response. An arbitrary categorization of patients into phenytoin response categories stands published.[12]

Common adverse effects reported by patients are shown in Table 2. Gum Hypertrophy as an ADR in all cases fulfilled the criteria to be classified as certainly due to phenytoin. Peripheral neuropathy was detected in five cases, and in all the five cases, it fulfilled the criteria to be categorized as probably due to phenytoin. Morbilliform rash was likewise categorized to be certainly caused by phenytoin, and tremor was deemed to be possibly due to phenytoin. Irrespective of their severity, gum hypertrophy, peripheral neuropathy, morbilliform rash, and tremor were not serious adverse events as per CDSCO.

Ataxia was detected in three cases. Two patients recovered from ataxia due to phenytoin overdose (serum phenytoin concentration was above therapeutic range), and in both the cases, ataxia was assessed to be certainly caused by phenytoin. One patient persisted with ataxia for more than 2 years after discontinuation of phenytoin, and the causality of ataxia in this case was categorized to be possibly due to phenytoin as there was a strong possibility of cerebellar damage due to prolonged seizure. Nonetheless, ataxia in this patient was an AE associated with persistent significant disability or incapacity as the patient was unable to walk without support and hence a serious adverse event as per the CDSCO.

Pk data for 87 patients were subjected to final statistical analysis. Mean serum phenytoin trough (C_0) concentration was 12.105 ± 0.433 μg/ml. Mean serum phenytoin peak (C_4) concentration was 16.895 ± 0.571 μg/ml. Mean AUC_{0-4} was 57.99 ± 1.76 μg/ml/h. Shapiro–Wilk test revealed that the sample data for peak, trough, and AUC_{0-4} were normally distributed [Table 3].

Audit of 135 TDM requisitions revealed that 54 (40%) requisitions scored one and were graded as unacceptable; 34 (25%) requisitions scored two and were graded as of poor quality; 35 (26%) requisitions scored three and were graded as incomplete; 12 (9%) requisitions scored four and were graded as satisfactory; while none of the requisitions was found to have a score of five or complete.

DISCUSSION

PK monitoring commonly, though erroneously, known as "TDM" is considered useful in enhancing therapeutic benefits and minimizing the incidence of adverse effects of narrow therapeutic index drugs. It begins with a determination of an initial dosage regimen appropriate for the clinical condition in the context of patient demographic characteristics as age, body weight, organ function, and concomitant drug therapy. Conventionally, drug concentration measurements are needed for reasons like dosage adjustments secondary to changes in clinical state, toxicity monitoring, lack of therapeutic response, differentiating noncompliance from metaboliser status, differentiation of disease state from toxicity, assessment for drug interactions or guiding withdrawal of therapy.[13] Provision of appropriate information when requesting drug concentration measurement is essential to optimize interpretation of results and quality of feedback to the clinicians.[14] Measuring plasma concentration of

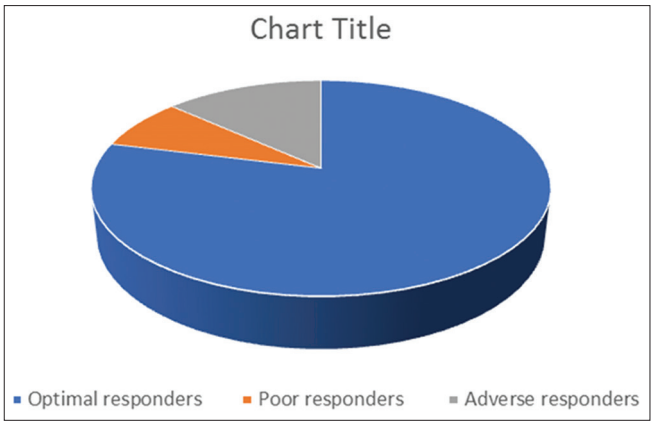

Figure 1: Case categorization of phenytoin pharmacodynamic response

Table 2: Common adverse effects reported by patients

Adverse effects	Number of instances
Gum hypertrophy	15
Forgetfulness	9
Generalized weakness	9
Headache	9
Tremor	7
Giddiness	5
Anxiety	5
Sleepiness	5
Peripheral neuropathy	5
Unsteadiness of Gait	3

Table 3: Average profile of phenytoin Pk parameters of participants (*n*=87)

Phenytoin Pk parameter	Mean±SD
C_0 (μg/ml)	12.10±0.433
C_4 (μg/ml)	16.89±0.57
AUC_{0-4} (μg/ml/hr)	57.99±1.76

Pk: Pharmacokinetic, SD: Standard deviation

all drugs is unnecessary, and it is prudent to employ drug concentration measurement only for drugs with narrow therapeutic range, marked PK variability, and when therapeutic and/or adverse effects are difficult to monitor. Conventionally, the best practice guidelines for TDM are ordering drug concentration measurements only when clearly indicated, conducting validated assays in appropriate biological matrices collected at recommended times relative to drug intake and finally providing assay results with meaningful interpretation on the basis of PK and clinical principles within useful time frames. As a rule biological matrix, essentially blood should be drawn at trough or just before the next dose (C_{min} and C_{pss}) in routine drug level measurements as trough levels are less likely to be influenced by variations in absorption, distribution, and elimination. Two main exceptions to this rule are toxicity monitoring and poor therapeutic control requiring loading doses when random or immediate sampling might be done.[15] Recently, the importance of incorporating pharmacovigilance and pharmacogenomic inputs to complement evidence generated by TDM has been underscored.[12,16]

Phenytoin continues to be used by a large population in the developing countries. Although largely replaced by valproate or carbamazepine for use in partial and secondarily generalized seizures, it retains its rank in the treatment of status epilepticus.[17-19] Classically a difficult to handle drug, due to changing kinetics at therapeutic doses, phenytoin therapy is further complicated by pathogenetically elusive adverse effects such as gum hypertrophy and cerebellar degeneration. The availability of CYP2C9, CYP2C19, and HLA B1507gene sequencing, if at all helpful, is largely confined to few centers and not practiced routinely, especially in this part of the world. Besides, there is a lack of large prospective clinical trials to determine whether the use of genotyping improves clinical outcomes despite evidence of a link between adverse effects and polymorphisms specifically CYP2C9 *2 and *3 in this context.[20] As such gene polymorphism-based recommendations might play a role in individualizing phenytoin therapy in newly diagnosed cases, these seem irrelevant in patients already maintained on phenytoin. In this backdrop, phenytoin seemed an ideal probe to reflect current practice and problems with TDM service. As phenytoin Pd analysis was done using an arbitrary scale, no study was available for the comparison of Pd analysis. The results of phenytoin Pk analysis were consistent with earlier results.[21]

A review of the literature reveals the importance of HLAB * 1502 allele and CYP2C9 genotype to phenytoin treatment outcomes.[22-26] Investigating these genes for personalization of phenytoin therapy can complement phenytoin TDM, especially as regard adverse effects which cannot be correlated to serum phenytoin levels. It might seem wise to withhold implementation of these recommendations pending more evidence for mild or moderate ADRs; however, the same attitude as regard serious ADRs begs some questions. Expedited reporting for serious ADRs is already in place, and it is high time that such pharmacovigilance initiatives should be taken further by some sort of sentinel reporting and investigating serious ADRs on a priority basis.

Another issue that continues to plague TDM utilization is the lack of recent literature supporting its cost-effectiveness. A given dose of drug does not produce the same plasma concentration in all patients as there are considerable variations in absorption, distribution, and elimination among people. The polymorphism of drug metabolizing genes has, by far, the greatest impact for inter-individual differences in drug response. This issue was historically addressed by TDM, which developed in the 80's, an era when hospitals were considered mostly as non-profitable organizations contrary to the current era when hospitals in private and public sector both are trying to run on a no gain no loss economy so to say the least. In the current scenario especially in super specialties like clinical pharmacology, the borders between research and healthcare are blurred and so the argument of cost effectiveness seems unrealistic. Furthermore, with the availability of high throughput genome sequencing and nanotechnology, one is tempted to overlook the experience gained by this time-tested though tedious resource. Nonetheless, TDM remains an important milestone toward personalization of treatment, especially for drugs such as lithium and phenytoin.

Drug assay procedures have evolved from a variety of analytical methods ranging from spectrophotometry to high-performance liquid chromatography.[27] Currently vast majority of drug assay procedures are some variant of immunobinding assay procedures such as fluorescence polarization immunoassay, EMIT, and enzyme-linked immunosorbent assay.[28]

As such, TDM continues to be a tertiary care investigation provided by centralized laboratories having enormous equipment that can be handled by trained personnel only. This adds to the cost and time involved for TDM further compromising its application for personalization of medicine. Nanopharmacological techniques such as microfluidic electrochemical detection for *in vitro* continuous monitoring for doxorubicin/kanamycin and a portable device for monitoring methotrexate by surface plasma resonance have opened doors for the development of real-time point-of-care testing for some of the drugs requiring TDM.[29] Extending such technological advances

to drugs such as lithium and phenytoin that classically required TDM and continue to be used by a large population remains the challenge to be taken up by medical and scientific communities.

An audit of TDM requisitions in our setting did not yield encouraging results. Authors propose a template which can be downloaded and modified for providing requisite information by or for TDM laboratories. Multidisciplinary educational approach, computerizing requesting methods, traditional and formal education for changing physician behavior, proactive approach on part of the clinical pharmacologists, and better advocacy arethe need of the hour for optimum utilization of this underutilized health-care resource.

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