Therapeutic Drug Monitoring of Antiepileptic Drugs at a Tertiary Care Hospital of Eastern Nepal

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ABSTRACT

Background

Therapeutic drug monitoring (TDM) is the process of measuring drug level in body fluids. It is done to maintain plasma concentration of the drug under therapy within a specific target range for maximum therapeutic efficacy without unnecessary exposure to adverse effects.

Objective

This study aims to evaluate necessity of therapeutic drug monitoring in Phenytoin, Carbamazepine and Lamotrigine therapy among epileptic patients.

Method

A prospective, cross-sectional study was conducted for a period of one year at BP Koirala Institute of Health Sciences, Dharan, Nepal. After taking detailed history, blood samples were collected from epileptic patients on monotherapy with the selected drugs. Plasma levels of these drugs were analyzed using High Performance Liquid Chromatography technique (HPLC). Out of total 42 selected patients, 21 were tested for phenytoin, 17 for carbamazepine and four for lamotrigine. The result was categorized into therapeutic, sub-therapeutic and above-therapeutic groups based on reference range.

Result

Out of total 21 samples tested for phenytoin, 15(71.4%) had plasma drug level within therapeutic range, 5(23.8%) had within subtherapeutic range and 1(4.8%) had above therapeutic range. Analysis of carbamazepine plasma level showed 14(82.3%) at therapeutic level, 1(5.9%) at sub-therapeutic level and 2(11.8%) at above-therapeutic level. Lamotrigine testing in four samples showed 2(50% in) both within therapeutic range and above-therapeutic range.

Conclusion

Therapeutic drug monitoring of phenytoin, carbamazepine and lamotrigine showed variation in plasma level irrespective of the therapeutic dose. It is suggested that dose adjustment of antiepileptic drugs should be done after establishing 'individual therapeutic range' following regular plasma monitoring.

KEY WORDS

Anti-epileptic, High performance liquid chromatography, Therapeutic drug monitoring

INTRODUCTION

Therapeutic drug monitoring (TDM) is the measuring of drug concentration in body fluids, mostly plasma or saliva. It is a concept of individualization of dosage in a way that plasma concentration can be maintained within a specific target range. The goal of TDM is to achieve adequate therapeutic response with minimal or no adverse effects by maintaining optimal plasma concentrations of drugs after application of pharmacodynamic and pharmacokinetic principles.[1] It is indicated for monitoring drugs with a narrow therapeutic index and non-linear pharmacokinetics and also for the drugs whose plasma concentration correlates well with clinical effect.[2] However, it is primarily done for checking compliance or toxicity in cases with poor treatment outcome, despite adequate medication.[3]

The first-generation antiepileptic drugs (AEDs) like phenytoin, carbamazepine and lamotrigine possess all the properties indicated for TDM. They have a narrow therapeutic index and complex pharmacokinetic properties.[4] A slight variation in the dose may cause marked fluctuation in plasma concentration leading to either loss of therapeutic efficacy or toxic effects. The development in technologies nowadays has helped to establish a close relation between the doses, plasma concentration and therapeutic response. The desired clinical response of many older AEDs is observed within the therapeutic range, whereas below or above therapeutic range are likely to produce insufficient seizure control or toxicity respectively.[5] Often prolonged exposure of phenytoin and carbamazepine at toxic plasma level may cause severe reversible or irreversible neurological and psychological complications and also exacerbate seizures.[6,7] Therefore, this study was conducted to investigate necessity of TDM of AEDs in epileptic patients.

METHODS

It was a cross-sectional study, carried out in Department of Clinical Pharmacology and Therapeutics, BP Koirala institute of health Sciences (BPKIHS), Dharan from August 2015 to July 2016 after obtaining ethical clearance from Institutional Review Committee of BPKIHS. Sample size was calculated to be 42, using formula, $n=Z^2p(1-q)/d^2$, Where Z=static constant corresponding to level of confidence, p=expected prevalence and d= precision or margin of error. Considering prevalence of 38% obtained from previous study in similar settings.[8] Sampling frame of 50 epileptic patients in past one year from records at BPKIHS, the sample size was calculated to be 38 with 5% margin of error (at 95% confidence interval, 80% power and Z= 1.96) and adding 10% to corrected sample size to minimize various biases. Convenience sampling method was used for selection of patients. Written consent was taken before conducting study. In case of minors, parents or accompanying local guardian signed the informed consent form. The inclusion criteria were epileptic patients of the specific age group 1 to 60 years, under treatment (on the selected drugs) for at least six months duration and visiting to the outpatient department of the hospital. The exclusion criteria were patients of extremes of ages (< 1 year and > 60 years), concomitant therapy with any other drugs, alcohol abuse, severe neurological or psychological disease, patients with ischemic heart disease (IHD), congestive heart failure (CHF), arrhythmia or dyslipidemia, patients with history of renal and hepatic impairment and pregnancy (confirmed or suspected).

Pre-dose EDTA (Ethylenediaminetetraacetic acid) blood samples (trough concentration) along with demographic details, drug history, seizure control, experience of adverse effects and other relevant history were acquired from the patients in semi-structured Proforma. Plasma was assayed using Reverse-phase High Performance Liquid Chromatography (HPLC) technique.[9] Liquid-liquid extraction procedure was applied for the extraction of analyte (selected drug) from plasma by using a suitable extractive solvent. The extractive solvent was tertiary butyl methyl ether for phenytoin and chloroform for carbamazepine and lamotrigine respectively. The extracted residue was further reconstituted using mobile phase (prepared with mixture of phosphate buffer and acetonitrile). The reconstituted fluid was injected into pre-validated HPLC machine (Knauer, Germany) working in reverse phase. A chromatogram was obtained. The plasma drug concentration was measured by calculating the area under the obtained curve at a particular retention time of the desired drug, using software from Knauer, Germany at the laboratory of Department of Pharmacology, BPKIHS. The entire chemicals used during analysis were from Merck, India.

The obtained result was categorized into: therapeutic group (within therapeutic reference range), sub-therapeutic group (below therapeutic reference range) and above-therapeutic group (above therapeutic reference range) based on their normal plasma therapeutic reference range (Phenytoin:10-20 µg/mL, carbamazepine: 4-12 µg/mL and Lamotrigine: 3-14 µg/mL).[10,11] Out of 42 blood samples, 21 were tested for phenytoin, 17 for carbamazepine and four for lamotrigine. The information obtained was compiled and entered in Microsoft Excel 2007. The descriptive statistics mean, standard deviation (SD), frequency and percentages were calculated using Statistical Package for Social Sciences (SPSS) version 11.5 and the results were presented in tabulated form.

RESULTS

Out of 42 patients, phenytoin was used in 21, carbamazepine in 17 and lamotrigine in 4 cases. Total males were 24(57%) with male and female ratio of 1.3. The majority of patients belonged to age group 11-20 years with mean age of 23.5±14.4 years (Table 1).

Phenytoin was used in half (50%) of the patients in our study sample. It was used in children below fourteen years to adult of forty-five years (Table 2). Patients were on daily maintenance dose of phenytoin ranging from 100 mg/day to 400 mg/day. Analysis of plasma level of phenytoin showed that 15(71%) patients had their plasma level within therapeutic range while 6(29%) patients had sub-therapeutic range (Table 2). The lowest level detected was 4.6 µg/mL in a 42 year male and highest level detected was 19.2 µg/mL in a 15 year male with mean serum concentration of 12.3±3.9 µg/mL. Twelve patients on phenytoin had good seizure control in the past one year (Table 5).

Table 1. Age and gender distribution of patients (n=42).

Age Group		N	%
Years	1-10	**6**	**14.3**
	11-20	11	26.2
	21-30	8	19.1
	31-40	7	16.7
	41-50	5	11.9
	51-60	1	2.4
Gender	Male	**24**	**57.1**
	Female	**18**	**42.9**

Table 2. Age distribution and serum phenytoin level (n=21)

Age*	Subtherapeutic (< 10 µg/mL)	Therapeutic (10-20µg/mL)	Above therapeutic range (> 20 µg/mL)
Children (n=8) (1-14 years)	4(19%)	4(19%)	0
Adults (n=13) (15-60 years)	1(4.8%)**	11(52.4%)	1(4.8%)

*patients were divided into pediatric (<14 yrs) and adult age group (>14 yrs) during analysis
**Lowest level detected was 4.6 µg/ml in a 42 yrs male

Carbamazepine was used for seizure control in 17 cases in both pediatric as well as adult age group (Table 3). The minimum prescribed carbamazepine dose for maintenance therapy was 200 mg/day and maximum dose was 600 mg/day. Its plasma level was within therapeutic range in 14(82%), sub-therapeutic in 1(6%) and above-therapeutic in 2(12%) cases. It was the only drug in our study whose levels were in all the three categories. The lowest level detected was 2.5 µg/mL seen in a 12 year male and highest level detected was 18.1 µg/mL in a 16 year male with mean serum concentration of 10.9±3.5 µg/mL. The patients who were in above-therapeutic group had complaints of excessive drowsiness, vertigo and decreased appetite along with poor seizure control.

Lamotrigine was predominantly used in patients of the pediatric age group (Table 4). The daily maintenance dose ranged from 25 mg/day to 75 mg/day. Serum analysis showed equal numbers of lamotrigine users in both the therapeutic and sub-therapeutic category (Table 4). Two

Table 3. Age distribution and serum carbamazepine level (n=17)

Age*	Subtherapeutic (< 4 µg/mL)	Therapeutic (4-12µg/mL)	Above therapeutic range(> 12 µg/mL)
Children (n=4) (1-14 years)	1(5.9%)**	3(17.6%)	0
Adults (n=13) (15-60 years)	0	11(64.7%)	2(11.8%)£

*patients were divided into pediatric (<14 yrs) and adult age group (>14 yrs) during analysis
**Lowest level detected was 2.5 µg/ml in a 12 yrs male, £Highest level detected was 18.1 µg/ml in a 16 yrs male

Table 4. Age distribution and serum lamotrigine level (n=4)

Age	Subtherapeutic (< 3 µg/mL)	Therapeutic (3-14µg/mL)	Above therapeutic range(> 14 µg/mL)
Children (n=4) (1-14 years)	2(50%)	2(50%)	0

Table 5. Seizure control status of patients.

	Seizure controlled n(%)	Seizure uncontrolled n(%)
Phenytoin (n=21)	12(57.1)	9(43)
Carbamazepine (n=17)	9(53)	8(47)
Lamotrigine (n=4)	2(50)	2(50)

patients on lamotrigine had good seizure control in the past one year while remaining two patients had experienced seizure the past one week to one month (Table 5).

Most of the patients 23(55.8%) were seizure free in the past one year with the selected drugs and remaining 19(45.2%) had history of seizure in the past one week to one month, irrespective of maintenance dose and serum concentration (Table 5).

DISCUSSION

Therapeutic drug monitoring (TDM) is an age old practice of measuring various drugs with complex pharmacokinetic and pharmacodynamic properties. It is based on the basic assumption that concentration of the drug being measured correlate with the concentration at the target site of action (e.g. brain). The principle of TDM was developed in 1960s. It has evolved from a luxury to necessity attributable to the advances in research and administration of sophisticated laboratory instrument as well as methods.[3,12]

Monitoring of AEDs has few challenges.[12] Firstly, seizure occurs irregularly, sometimes after a long gap between the episodes. As a result, to assess the clinical benefit of AED therapy, a long-term observation may be required. Secondly, adverse effects produced by some AEDs may mimic the underlying neurological disorder making it difficult to understand the inefficacy of undergoing medical treatment or worsening of medical condition. Lastly, there is no available laboratory investigation or

diagnostic procedures to assess the clinical efficacy of AEDs.[10] The most common reason for employing TDM for AEDs is that these drugs shows variable and/or often unpredictable pharmacokinetics related to differences in drug metabolism.[4,12] In this study we investigated necessity of TDM in the older antiepileptics like phenytoin, carbamazepine and lamotrigine.

In our study, male epileptic patients outnumbered females. This finding was consistent with other similar studies conducted in Nepal and our neighboring country India.[8,13] The reason may be attributed to two major issues. Firstly, epilepsy is considered as social stigma in developing countries like ours because of the lack of knowledge and social awareness. Female sufferers and their parents tend to keep silent regarding their medical condition fearing future outcomes. Secondly, it may be due to the prevalence of existing socio-cultural mindset facilitating male patients for better healthcare facilities than females, leading to higher diagnosis in them.[14,15]

In our study population phenytoin was used in majority of patients including both pediatric and adult age groups. Though an older AED, it is still widely used. It is the drug of choice for treatment of epilepsy due its action against both partial and generalized seizures, easy availability of both adult and pediatric formulations and low cost.[16] The serum drug analysis of phenytoin in our study showed to be within therapeutic range in majority of patients. The findings of TDM of phenytoin in various studies are different.[6,17-19] In the study conducted by Shakya et al. out of 81 samples tested for phenytoin, only 35.8% cases had in therapeutic level. Majority (64.4%) were at sub-therapeutic level or toxic level (28.4%).[8] In another study by Gerg et al. out of 116 samples tested for phenytoin, 38(32.8%) were at therapeutic level, 63(54.3%) at subtherapeutic level, 12(10.3%) at toxic level and 3(2.6%) were at non-detectable levels.[17] The reason may be due to differences in patient selection, sampling techniques and analytical methods. The other reason may be due to pharmacological properties of phenytoin itself. It is absorbed completely following oral administration and bound extensively to plasma protein (albumin). The pharmacological action is produced by unbound (free) drug only.[18] Any medical condition that alters the plasma protein level (e.g. uremia, renal failure or liver disease, etc.) or presence of drugs that replaces phenytoin from protein binding site can change the plasma level of phenytoin.[18] Further, phenytoin is notorious for interaction with many drugs, when co-administered. As such, interaction with drugs (drug-drug) or disease (drug-disease) may cause changes in phenytoin pharmacokinetics, leading to changes in efficacy and/or toxicity.[4,18,19] However, in this study we have tried to minimize above condition but possibility cannot be entirely ruled out.

In our study, it was interesting to find that patients on maintenance therapy with phenytoin at 400 mg/day had his serum level within therapeutic range with good seizure control. While some patients on maintenance therapy with phenytoin at 100 mg/day had their plasma level at therapeutic range and some had sub-therapeutic range. Both of the above groups had poor seizure control irrespective of their plasma level. This can be explained by the fact that phenytoin exhibits non-linearity in pharmacokinetics even within therapeutic ranges. The enzyme system involved in phenytoin metabolism becomes gradually saturated leading to decrease in rate of elimination as the dose is increased.[20] Once metabolizing enzyme is saturated, a small change in therapeutic dose may lead to large change in phenytoin level. The phenytoin concentration leading to enzyme saturation shows pharmacogenetic variation among individuals.[18,20] Thus, patients taking phenytoin at same dosage can have different plasma phenytoin because of inter-individual variability. Furthermore, difference in dosage forms or salt form (phenytoin sodium or phenytoin base) and/or two brands may also lead to changes in bioavailability of phenytoin.[18-20]

In our study carbamazepine (CBZ) was in therapeutic range in 14(82.3%), sub-therapeutic in 1(5.9%) and above-therapeutic in 2(11.8%) cases. In a study done by Garg et al. CBZ was in therapeutic range in 93(75.6%), sub-therapeutic in 22(17.9%) and at toxic (above-therapeutic) level in 3(2.4%) cases.[17] In the study by Shakya et al. CBZ was observed to be within therapeutic range in 191(79.3%), subtherapeutic in 38(15.8%) and above therapeutic in 12(4.9%) cases.[8] On the contrary, findings by Nadkarni et al. showed CBZ level within therapeutic in 6(67%), sub-therapeutic in 2(22%) and none at toxic level.[21] This variability may be due to difference in validated therapeutic range in different laboratories. The other cause may be due to pharmacological properties of CBZ. Like phenytoin, CBZ also exhibit complex pharmacodynamic and pharmacokinetic properties. Used since 1965 for treatment of partial seizure with or without secondary generalization, CBZ is well absorbed following oral administration and bound to plasma proteins. However, its absorption is delayed by large doses given at same time. Any medical condition that can change plasma protein level may change the free plasma level of the drug and affect therapeutic efficacy.[4,22] The metabolism of CBZ is quite complex. It is metabolized to carbamazepine 10,11-epoxide, the metabolite having anticonvulsant properties similar to parent drug. In chronic therapy plasma concentration of free metabolite may reach up to 50% of parent drug. Monitoring CBZ is usually done by various immunoassays having specificity to parent drug and its metabolite, contributing to substantial therapeutic effect.[11] CBZ is strong inducer of liver-drug metabolizing enzyme (CYP3A4), which metabolizes other drugs as well as itself. This property of CBZ is known as 'autoinduction.' Normally the duration for which CBZ stays in plasma ranges to 20-40 hrs but due to 'autoinduction' it is lowered to 10-20 hrs in chronic therapy. Further, there is large inter-individual variation in metabolizing enzymes. Besides, like other first generation AEDs neurological side effects of CBZ

are common when plasma level surpasses 9 mg/L which may mimic underlying neurological disorder and may affect clinical decision. All of the above characteristics of CBZ make it a strong candidate for TDM.[11,22]

Lamotrigine is a newer antiepileptic in our setup, used in few cases till date. In our study, there were four cases of lamotrigine. It was used only in pediatric age group. Serum analysis showed result distributed in therapeutic and sub-therapeutic groups equally. Contrary to the study done by Kadam et al. in pediatric population, majority was in therapeutic group compared to sub-therapeutic and toxic groups.[23] In our study seizure was well controlled in patients under therapeutic dose while it was uncontrolled in the subtherapeutic group irrespective of prescribed doses. Though a newer antiepileptic, it has properties similar to phenytoin and carbamazepine.[12] There is large inter-individual variability in metabolizing enzymes and drug-drug interactions when co-administered.[10,23-26] It may have affected the result of TDM. Though we have tried to rule out the chances of drug-drug interactions by exclusion criteria, possibility of inter-individual variability in metabolizing enzymes cannot be entirely ruled out.

Although reasonably well-defined therapeutic ranges (target range) have been established for most AEDs, it does not fit for all. The large inter-individual differences in pharmacokinetics make treatment challenging for AEDs. It is difficult to predict the optimum dose for a particular patient because some patients can have good seizure control at serum concentration below target range, while other patients may exhibit concentration-related side effects within the normal range.[12] It is not recommended to increase the dose of AEDs if patient remains seizure free at sub-therapeutic range. Conversely, the dose should be lowered in patients exhibiting sign and symptoms of toxicity being at therapeutic ranges. It advocates the importance of establishing 'individual therapeutic range' for different patients. TDM plays important role in guiding the treatment in an effective way in the face of unpredictability of AEDs.[27]

This study can be useful in clinical practice as it highlights the fact that same therapeutic doses of a particular drug may achieve different plasma concentrations in different individuals. The dose should be adjusted on the basis of clinical response rather than plasma concentration for minimization of daily drug exposure with minimal or no adverse effect and adequate clinical outcome.

The findings of this study need to be interpreted in the presence of some limitations. Small sample size, one-time study and convenience sampling methods may be the source of possible biases. A large, longitudinal study is needed before coming to any strong conclusion.

CONCLUSION

This study of therapeutic drug monitoring of phenytoin, carbamazepine and lamotrigine showed variation in plasma level. Therapeutic, sub-therapeutic and even above-therapeutic ranges were observed irrespective of therapeutic dose. It is suggested that dose adjustment of antiepileptic drugs should be done only after establishing 'individual therapeutic range' for different individuals taking into consideration of inter-individual variation of pharmacokinetics, after regular therapeutic monitoring of antiepileptic drugs. It ensures minimum exposure of patients to adverse effects, better patient compliance and appropriate clinical outcome.

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