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Research Article

OPTIMIZATION AND ASSESSMENT OF TDM AT TERTIARY CARE: AN INDIVIDUALIZATION PROCESS

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ABSTRACT

Epilepsy is a chronic disease that may require antiepileptic drug (AED) therapy. TDM is a process which starts from taking the sample from the patient till its interpretation of results. A single quantifiable value of drug level in a patient makes the dosage regimen in chronic therapies when narrow therapeutic drugs are used. It is the goal of TDM to use drug concentration to manage a patient's medication regimen and optimize outcome. Clinicians routinely monitor pharmacodynamics by directly measuring physiological indices of therapeutic responses e.g. lipid concentrations, blood glucose, blood pressure, clotting tests. For many drugs there is either no readily available measure of effect or it is insufficiently sensitive. It is an integral part of pharmacotherapy which starts from the decision to request a drug level in a biological sample in a clinical laboratory and is followed by clinical interpretation for the validity of therapeutic management. Commonly used conventional antiepileptic drugs are Phenytoin, Carbamazepine, Valproic acid, Phenobarbitone. These drugs have complex pharmacokinetic properties leading to fluctuate their serum concentration in the systemic compartment at a given therapeutic dose. The present study was done along with the lithium to integrate their therapeutic, subtherapeutic and toxic concentratinos retrospectively. 855 levels of blood samples were tested, 76 were inconclusive comprising of 8.9%. Out of total 275 lithium samples 80% were in the therapeutic range of 0.3 to 1.2 mEq/Litre. 250 samples of Phenytoin were assessed and 41.20% had therapeutic level. 106 samples of Carbamezepine had a varied percentage of sub-therapeutic, therapeutic and toxic levels. Only 3.77% of levels were above 12 micrgram/ml and 16.03% levels were inconclusive. Out of 151 levels of Valproic acid 50.98% levels fall between 70-90 microgram/ml. Although phenobartritone is not prescribed commonly only 73 samples were assessed and 47.94% comprised in the therapeutic range of 10-20 microgram/ml.

Keywords: Methi, standardization, HPTLC, Heavy metals, evaluation, Physiochemical parameters.

Abbreviations: *TDM= Therapeutic Drug Monitoring, EMIT= Enzyme Multiple Immuno Technique, AED= Anti-Epileptic Drugs.*

INTRODUCTION

Epilepsy is a chronic disease that may require antiepileptic drugs (AEDs) therapy for many years. The efficacy of AED monotherapy in the treatment of epilepsy is well established. Approximately 60-70% of new diagnosed patients will have their seizure controlled effectively by one AED, and switching to an alternative nature AED will offer effective seizure control in upto half of the 30-40 % of patients. AED polytherapy may be helpful for a small population of patients who do not respond to monotherapy but careful consideration should be given to the consequences of any drug interactions between the various AEDs that are co-administered. Indeed, it has been estimated that in 60% of patients experiencing AED intoxication, a drug interaction was the cause.[1] Many excellent articles describing TDM and limitations of therapeutic ranges have been published [2]. Patients in the wider community are managed by their doctors utilizing biochemical laboratories, often without clinical interpretation of the drug concentration measured. Phenytoin is one of the most widely prescribed AEDs in the USA. 52% of AED prescriptions are of Phenytoin compared to 19% for Valproic acid, 11% Carbamazepine and 7% Phenobarbital. ADRs to Phenytoin generally fall into two categories: dose or concentration dependent toxicities and hypersensitivity reactions

that are idiosyncractic in nature. [3] Therapeutic ranges are recommendations derived by observing the clinical reactions of a small group of patients taking the drug. The lower limit (trough) is set to provide ~50% of the maximum therapeutic effect, while the upper limit (peak) is defined by toxicity, not therapeutic effect. It is not unusual for some patients to achieve therapeutic effects at levels below the established range. Others may experience toxicity while still in the established range. [4,5]

The factors that affect result interpretation vary from drug to drug. For example, digoxin concentration must be interpreted in light of the creatinine and potassium concentrations, the presence of acidosis or the administration of interacting drugs as well as the patient's clinical state.2 When determining the appropriate lithium dose or interpreting lithium results, knowing if a women is pregnant is key, as dose requirements increase due to increased renal clearance.[6] Whole plasma drug concentrations are most often measured. Unbound plasma concentrations may be requested when a physician suspectsthat the patient's protein binding capacity for the drug may be altered due to pregnancy, disease, malnutrition, or drug interaction.[7] The drug concentration is complementary to and not a substitute for clinical judgement so it is important to treat the individual patient and not the laboratory value. Drug concentrations may be used as surrogates for drug effects so therapeutic drug monitoring may assist with dose individualization. It can also be used to detect toxicity, so therapeutic drug monitoring can optimise patient management and improve clinical outcomes. Careful selection of drugs to be monitored should occur. Regular monitoring of many drugs is not required in a clinically stable patient.[8] Evidence indicates a pattern of increasing awareness and caution when using a drug of narrow therapeutic range like lithium. TDM for lithium definitely places an additional economic burden on the patient as well as health care providers TDM-assisted psychiatric treatment is potentially useful and cost effective in decreasing the ADR and preventing lack of response[9]. Some patients only require low phenytoin concentration to attain complete seizure control, while others obtain benefit from concentrations greater than 20 microgram/ml without adverse effects. The variability may be due to seizure type, the severity of the under lying disorder, or to genetic abnormalities [10]. The correct timing of sampling is important for accurate TDM. For most drugs the "target" concentrations are based on steady state samples taken at specific times after the dose. In most clinical situations, the attainment of steady state can be assumed 3 to 5 half-lives after change in dose or initiation of therapy provided that the dose and clearance remain constant (unless loading doses are given). For most drugs, plasma samples should be taken just before the next dose (trough) as these levels are less likely to be influenced by absorption and distribution problems.[11] The plasma drug concentration may be rendered difficult by the presence of metabolites with therapeutic or toxic activity. If active metaboloites are produced both the parent drug and the metabolites would have to be measured to provide a comprehensive picture of the relation between the total plasma concentration of active compounds and the clinical effect.[12].Appropriateness of sampling and indication for serum drug concentration monitoring needs to be improved . A pharmacist in a tertiary care hospital ward can revolutionize the TDM service by conducting clinical rounds on patient care so that appropriateness of indications and sampling can be performed consistently. [13]

MATERIALS & METHODS

A retrospective observational study was conducted in the department of Clinical Pharmacology. Randomized levels of the patients, who were on these drugs from July 2008 to July 2013, were assessed. Only those patients were included who were on usual therapeutic doses of one or two combined AEDs drugs for 3-4 months, taking same dose with equal intervals. Equal male and female were included from the age group of (6-60 years) Serum levels of these AEDs were analyzed by EMIT system using Semi-automatic Analyzer and lithium was analyzed by Flame photometry. The EMIT (Enzyme Multiplied Immunoassay Technique) homogeneousenzyme immunoassay is a versatile methodology designed to measure microamounts of drugs in human biological fluid (serum).The EMIT technology is based on competition for the target analyte antibody binding sites. Analyte in the sample competes with the drug in the enzyme reagent that is labeled with G6PDH. Active enzyme G6PDH converts the coenzyme (NAD) in the antibody reagent to NADH, resulting in a kinetic absorbance change that is measured Spectrophotometrically. Calibrators of AEDs were used to validate the levels and lyhyphocheck controls of all the three

levels (low, medium and high) were used to validate the method. 855 levels of blood samples were tested, 76 were inconclusive comprising of 8.9%. Out of total 275 lithium samples, 80% were in the therapeutic range of 0.3 to 1.2 mEq/Litre. 250 samples of Phenytoin were assessed and 41.20% had therapeutic level. 106 samples of Carbamezepine had a varied percentage of sub-therapeutic, therapeutic and toxic levels. Only 3.77% of levels were above 12 micrgram/ml and 16.03% levels were inconclusive. Out of 151 levels of Valproic acid 50.98% levels fall between 70-90 microgram/ml. Although phenobartritone is not prescribed commonly only 73 samples were assessed and 47.94% were comprising in the therapeutic range of 10-20 microgram/ml

RESULTS

Out of total 855 TDM samples, 76 were inconclusive tests comprising of 8.9%. 275 samples were tested for litium, 250 for Phenytoin, 106 for Carbamazepine, 151 for Valproic acid and only 73 tests were performed for Phenobarbitone Table 1.

Table 1: Total No. of TDM Samples

Drugs	Total No. of Samples	Inconclusive Samples
Lithium	275	10
Phenytoin	250	19
Carbamazepine	106	17
Valproic Acid	151	10
Phenobarbitone	73	10
Total:	**855**	**76**

Lithium tested in 275 samples showed that 0.3-1.2 meq/litre comprised of79.99%, 1.2-1.5 meq/litre comprised of 9.09% and less than 0.3 meq/litre or subterapeutic comprised of 6.18%. Interpretation of of 10 samples comprised of only 3.63% were inconclusive because of DDIs or of sampling error Table 2.

Table 2: Total No. of Lithium Samples

Concentration meq/litre	Total No. of Samples with %
0 - 0.3	17 (6.18)
0.3 – 0.6	48 (17.45)
0.6 – 0.9	72 (26.18)
0.9 – 1.2	100 (36.36)
1.2 – 1.5	25 (9.09)
>1.8	3 (1.09)
Inconclusive	10 (3.63)

Out of total 250 samples for Phenytoin only 41.20% of samples fall in the documented therapeutic range 20-40 micrigram/ml, 34.40% fall in sutherapeutic, 16.80% fall in toxic range and 7.60% were not interpreted correctly. Phenytoin levels are difficult to interpret because of saturation kinetics which starts from 10 microgram/ml only.Phenytoin has been used as monotherapy in adult population since its use as an antiepileptic Table 3.

Table 3: Total No. of Phenytoin Samples

Concentration µg/ml	Total No. of Samples with %age
0-5	55 (22)
5-10	31 (12.4)
10-15	63 (25.20)
15-20	40(16)
20-25	19(7.6)
25-30	10(4)
>30	13(5.2)
Inconclusive	19 (7.6)

A total of 106 samples of carbamazepine were included in this study. 47.17% comprised of 50 samples were in the therapeutic range of 4-8 microgram/ml in this population. 16.03% of samples were not interpreted because of not estimating its metabolite 10, 11 epoxide which is itself an active metabolite. EMIT is not an ideal method for the estimation of carbamazepine and its metabolite because of interference in estimation process Table 4.

Table 4: Total No. of carbamazepine Samples

Concentration µg/ml	Total No. of Samples with %age
0-2	7 (6.6)
2-4	10 (9.43)
4-6	20 (18.87)
6-8	30 (28.3)
8-10	10 (9.43)
10-12	8 (7.54)
>12	4 (3.77)
Inconclusive	17

Therapeutic range of Valproic acid from 50-100 microgram/ml was found in 71.43% of samples. Maximum % of samples were determined from 70-90 microgram/ml therapeutic range, comprised of 50.98%. Less than 10% levels were sub-therapeutic, toxic and inconclusive. Valproic acid is devoid of enzyme induction but its metabolite contributes both as

antiepileptic as well as hepatotoxic. LFT of the patients may always be carried along with the drug estimation when the drug concentration remains above 100microgams/ml Table 6.

Only 73 samples of Phenobarbitone were requested in these 4 years at tertiary care and prescription of this drug has fallen because of its toxic potential and newer second generation drugs have been launched into the market. 69.84% samples fall in the therapeutic range of 10-40 microgram/ml and 13.69%

Table 5: Total No. of Valproic acid Samples

Concentration µg/ml	Total No. of Samples with %age
<50	8 (5.29)
50-60	16 (10.59)
60-70	10 (6.62)
70-80	43 (28.47)
80-90	34 (22.51)
90-100	20 (13.24)
>100	10 (6.62)
Inconclusive	10 (6.62)

comprise of only 10 samples were not interpreted because of sampling errors Table 7.

Table 6: Total No. of Phenobarbitone Samples

Concentration µg/ml	Total No. of Samples with %age
0-10	7 (9.58)
10-20	35 (47.94)
20-30	9 (12.32)
30-40	7 (9.58)
>40	5 (6.84)
Inconclusive	10 (13.69)

CONCLUSION

All these drugs are commonly prescribed to control the epilepsy and Phenytoin is an important armamentarium to control general tonic clonic as a monotherapy. There is a need to use newer methods to estimate the drug levels on a routine basis so as to validate the levels individually to lessen the adverse drug reactions and maximize the efficacy of such drugs having narrow therapeutic index and the cause of levels having inconclusive interpretation were sorted out. Drug interactions are a major problem in combination drug therapy. Although many of the predisposing factors that determine whether an interaction will occur are known in practice, it is still very difficult to predict exactly what will happen when an individual patient is administered two drugs that have the potential to interact. [14] Stopping medication can cause adverse effects like Carbamezepine and Phenytoin when Carbamazepine is stopped, during concurrent administration of an inducer, the object dose may be titrated to maintain therapeutic effect. If the inducer is discontinued, the induction will slowly dissipate and metabolism of the object drug will return to normal. If the dose is not reduced, toxicity may occur. [15] TDM is important to individualize the dosage regimen as per the individuals age, gender, disease, concomitant drugs, environment etc. TDM is not to estimate the level by selecting a good method only but it starts by taking the sample at appropriate time till its interpretation of results.

Drug level monitoring is a useful tool for assessing the efficacy or toxicity of drugs with narrow therapeutic indices. Drug levels should be interpreted in conjunction with an evaluation of patient parameters and not relied upon as the sole indicator of response. Numerous factors can influence drug levels and their interpretation. Inappropriately drawn or interpreted levels may result in suboptimal drug therapy and unnecessary expense to the patient. Correct interpretation of drug levels requires at least a consideration of the dosage form, the timing of the dose in relationship to the timing of the blood sample concomitant drugs, and the presence of disease. A clinical pharmacist, the Drug Information Center, or the pharmacy can be contacted for more information regarding specific drug level monitoring techniques, assistance in the interpretation of drug levels, or pharmacokinetic individualization of drug dosing.

Doctors can never assume that a drug will produce the desired effect in a patient. The value of measuring the plasma concentration of some important drugs, will allow the doctor to tailor the treatment to the patient, monitor the compliance, diagnose under treatment or toxicity, and detect drug interaction. The responsibility lies on physicians to follow the patient's progress and to monitor the response to a drug. [16]

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