Therapeutic Drug Monitoring of Antiepileptic Drugs

Shakya G,[1] Malla S,[2] Shakya KN,[3] Shrestha R [2]

[1]Department of National Public Health Laboratory, [2]Department of Pediatrics, [3]Department of Medicine, Kathmandu Medical College, Kathmandu, Nepal

ABSTRACT

Commonly used conventional antiepileptic drugs for pharmacotherapy in epilepsy are phenytoin, carbamazepine and valproic acid. These drugs have complex pharmacokinetic properties leading to fluctuation in their plasma level at given same therapeutic dose. The present study was done to monitor their plasma levels.

A prospective observational study was conducted at Natoinal Public Health Laboratory. After taking detail history, blood samples were taken from epileptic patients of all age groups and both gender who were on usual therapeutic dose of one or two combined antiepileptic drugs. Plasma level of these drugs were analyzed by using Fluorescence Polarization Immuno Assay (FPIA) technique. Out of total 417 testing, 81were tested for phenytoin , 241 for carbamazepine and 95 for valproic acid. Their levels were further analyzed to find therapeutic, subtherapeutic and toxic levels.

Out of total 81 blood samples tested for phenytoin, 38.8% had plasma drug at therapeutic level, 38.8% at subtherapeutic level and 28.4% had toxic level. Carbamazepine was tested in 241 samples and 79.3% cases had at therapeutic drug level, 15.8% had subtherapeutic drug level and 4.9% had toxic level. Out of 95 samples tested for valproic acid, 62% had therapeutic level and 20% had subtherapeutic and 18% had toxic level of drug.

Therapeutic drug monitoring of phenytoin showed wide fluctuation in its plasma level. Its toxic and subtherapeutic levels were quite high. It is suggested that the dose of phenytoin should be adjusted after regular plasma level monitoring only. Monitoring of carbamazepine and valproic acid were also helpful when their toxicity and efficacy are doubtful.

Key Words: *antiepileptic, drugs, epilepsy, monitoring, therapeutic*

INTRODUCTION

Phenytoin, carbamazepine and valproic acid are the commonly used conventional antiepileptic drugs (AED for pharmacotherapy in epileptic patients.[1] Therapeutic drug monitoring (TDM) of their blood levels are useful to check compliance and to confirm suspected toxicity. Phenytoin was introduced in 1938, carbamazepine in 1962 and valproic acid in 1978 as AEDs.[2-4] All of those exhibit non-linear kinetics. Carbamazepine and valproic acid have relatively short half lives. Phenytoin and carbamazepine cause enzyme induction whereas

Correspondence:
Dr. Geeta Shakya
National Public Health Laboratory
Teku, Kathmandu, Nepal
Phone: +977-9841240312
Email: nphl@wlink.com.np

valproic acid cause enzyme inhibition. These have complex pharmacokinetic properties leading to wide fluctuation in their plasma concentration, interaction potential with other drugs and narrow therapeutic index (phenytoin and carbamazepine) which can lead to toxic effects or loss of therapeutic efficacy.[5,6] Monitoring of phenytoin is particularly essential. Long term repeated exposure to high concentration of phenytoin may also predispose patients to irreversible neurotoxicity and may exacerbate seizures.[7] Hence, the present study was conducted to monitor the plasma level of these drugs.

MATERIAL AND METHODS

A prospective observational study was carried out at Natoinal Public Health Laboratory (NPHL) from Jan 1, 2007 to Jun 31, 2007. It included epileptic patients of both gender and age groups, ranging from 11 months to 90 years who were on usual therapeutic dose of one or two antiepileptic drugs and attended NPHL for drug analysis. A detailed history about epileptic fit and medication of AED was obtained from those who were willing to give informed consent to participate in the study. The exclusion criteria was the epileptic patients on treatment giving history of relapse of fit in last one month and having suspected signs symptoms of toxicity. As per recommendation, blood samples were collected from 382 epileptic patients, in the morning before the first daily dose of medication.[8] The plasma was assayed for phenytoin, carbamazepine and valproic acid by using Fluorescence Polarization Immuno Assay (FPIA) technique. Since 35 patients were on combination of two drug therapy, three samples were tested for phenytoin and carbamazepine, three for phenytoin and valproic acid and 29 for carbamazepine and valproic acid Out of total 417 testings, 81 were tested for phenytoin, 241 for carbamazepine and 95 for valproic acid. The information was compiled in Microsoft Excel system and data was analysed using Statistical Win Pepi programme. The results were further categorized according to serum level of drugs (Subtherapeutic level, therapeutic range and toxic level), age and sex.

RESULTS

Out of total 417 TDM testings 81 were tesed for phenytoin, 241 for carbamazepine, 95 for valproic acid, 29 for carbamazepine and valproic acid, 3 for phenytoin and carbamazepine and 3 for phenytoin and valproic acid. Mean age was 27.42. M:F ratio was 1.9:1. Phenytoin tested in 81 cases showed that 64.4% were in either subtherapeutic level (35.8%) or toxic level (28.4%). In only 35.8% cases had serum drug at therapeutic level (Table 1). Phenytoin had been found to be commonly used in adult age group between 16 to 60 years as compared to children group (Table 2). Carbamazepine had achieved therapeutic level in highest percent of cases, 79.3 %. It was found to be equally used in both adult and children age groups (Tables 3,4). The use valproic acid was also found in high percent of cases, 62% which included both adult and children.(Tables 5,6)

Table 1. Serum Phenytoin level (n-81)

Phenytoin level*	No
Sub therapeutic level (<10μg/ml)	29 (35.8%)
Therapeutic level (10 – 20 μg/ml)	29 (35.8%)
Toxic level (>20μg/ml)	23 (28.4)

*Lowest level detected was 0.49 μg/ml (23/F). Highest level detected was 55.28 μg/ml (61/M)

Table 2. Age distribution of patient taking Phenytoin (n=81*)

Age group in years	No
<1-15	8 (9.9%)
16-30	36 (44.4%)
31-45	20 (24.7%)
46-60	10 (12.4%)
61 and above	7 (8.6%)

Table 3. Serum Carbamazepine level (n=241)

Carbamazepine level*	No
Sub therapeutic level (<4μg/ml)	38 (15.8%)
Therapeutic level (4- 12 μg/ml)	191 (79.3%)
Toxic level (>12 μg/ml)	12 (4.9%)

*Lowest level detected was 0.23 μg/ml (20 yrs F). Highest level detected was 19.74 μg/ml (90 yrs F)

Table 4. Age distribution of patients on Carbamazepine (n=241*)

Age group in years	No
<1-15	86 (35.7%)
16-30	87 (36.0%)
31-45	41 (17.0%)
46-60	21 (8.8%)
61 and above	6 (2.5%)

DISCUSSION

The result revealed that carbamazepine was used predominantly in 57.8% of all epileptic patients. Its use was seen in both the youngest patient of 11months and

oldest patient of 90 years. Therapeutic level of drug was found in well appreciated proportion of patients taking carbamazepine 79.3% and valproic acid 62% when compared to those taking phenytoin 35.8%.

Table 5. Serum level of Valproic acid (n = 95)

Valproic acid level*	No
Sub therapeutic level (<50μg/ml)	19 (20%)
Therapeutic level (50- 100 μg/ml)	59 (62%)
Toxic level (>100 μg/ml)	17 (18%)

*Level unrecordbly very low (15 F). Highest level detected was 410 μg/ml (30 yrs F)

Table 6. Age distribution of patients on Valproic acid (n = 95*)

Age group in years	No
〈1-15	35 (37%)
16-30	35 (37%)
31-45	17 (17.6%)
46-60	8 (8.4%)
61 and above	0

Out of 81 blood samples tested for phenytoin 35.8% of patients only had therapeutic level of drug and was comparable to 32.8% found by Garg SK et al in their study.[5] But higher proportion of patients on phenytoin had serum drug level either at sub therapeutic level 35.8% or at toxic level 28%. The cause of it could be in terms of physicochemical characteristics of the drug, saturable kinetics as well as problem of bioavailability.[5] The other cause which could attribute to increase or decrease in serum level of phenytoin could be co-administration of other drugs along with phenytoin. Drugs which increase serum phenytoin level include: chloramphenicol, tolbutamide, acute alcoholic intake, salicylates, diazepam, estrogen, chlordiazepoxide, sulfonamides, ethosuximide, cimetidine and halothane etc. The drugs which decrease phenytoin level include: carbamazepine, chronic alcohol abuse, reserpine etc.[9] Phenytoin when used in combination with either carbamazepine or valproic acid, it was found that its level was in either sub therapeutic or toxic level. Phenytoin can extensively bound to plasma protein and can be subjected to displacement by other drugs, which compete for their binding sites. Many acidic drugs eg salicytates, sodium valproate, some non steroidal anti inflammatory drugs and warfarin could also strongly bind to albumin and displacement of phenytoin can occur. The main clinical problem arising from this type of interaction was that the fall in measured phenytoin may be misinterpreted as a need to increase drug and thereby increase the phenytoin toxicity.[10]

In 79.3% of patients taking carbamazepine had therapeutic level of drug and was similar to 75% found by Garg SK et al in their study. The drug was found in subtherapeutic level in 15.8% and toxic level in only 2.4% of patients. Carbamazepine also has complex physicochemical properties, short half life and narrow therapeutic index.[5] A variety of drugs could inhibit its metabolism increasing the risk of accumulation. Erythromycin and other macrolides were well recognized to cause significant elevation of carbamazepine concentration.[10] Large interindividual differences in apparent plasma half life linked to autoinduction and narrow therapeutic range make this drug suitable for monitoring.[10]

Therapeutic level of drug was found in 62% of patients taking valproic acid. But, 20% of patients had subtherapeutic level of drug while in 19% cases; the drug level was at toxic level. Of the main drugs used in the long term treatment of major epilepsies, only valproic acid was devoid of enzyme inducing properties, but a risk of interaction still existed as an inhibitor of oxidative and non oxidative drug metabolism.[12] As a result plasma level of it fluctuates during chronic treatment.[12] Metabolites of valproic acid contribute to both antiepileptic and hepatotoxic effects. Hepatoxicity may be fatal.[14] Considering all these effects, therapeutic monitoring of valproic acid is also quite useful.

This study will be useful in clinical practice as the same daily therapeutic dose of a particular drug lead to marked different blood concentration in different patients and this will affect the therapeutic response. In general, the dose of AED is increased depending on clinical response regardless of the serum drug level. The thorough drug level should be measured to provide a reference point for the maximum tolerated dose without toxicity symptoms. If seizures are poorly controlled, drug level in the blood should be measured after treatment is initiated, the dosage is changed or another drug is added for therapeutic regimen. Dose adjustment are then guided by the laboratory finding. The most common cause of lower concentration of drug than expected for the prescribed dose is poor patient compliances. Compliance can be improved by limiting to a minimum the number of daily doses and by regular monitoring the drug level.[15,16]

CONCLUSION

Therapeutic drug monitoring of phenytoin showed wide fluctuation in its plasma level. Its toxic and subtherapeutic levels were quite high. It is suggested that the dose of phenytoin should be adjusted after regularplasm level monitoring only. Monitoring of carbamazepine and valproic acid will also be helpful when their toxicity and efficacy are doubtful..

ACKNOWLEDGEMENT

Our thanks are due to all technical staff of therapeutic drug monitoring unit of National Public Health Laboratory, Teku for their technical support.

REFERENCES

1. Perucca E, Johannessen SI. The ideal pharmacokinetic properties of antiepileptic drug: How close does levetiracetam come. Epileptic disord 2003 May; 5 Suppl: 517-26.
2. Phenytoin: Drugs in pregnancy and breast feeding. [Online]. 2008 [cited 2008 Mar 20];[1 screen]. Available from: URL: http://drugsafetysite.com/phenytoin
3. Carbamazepine: Drug safety during pregnancy and breast feeding. [Online]. 2008 [cited 2008 Mar 20];[1 screen]. Available from: URL:http://Drugsafetysite.com/carbamazepine
4. Lisa KH, Philip AM. Valproic acid overdose and haemodialysis. Nephrol dial transplant 2001; 16:1483-86.
5. 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.
6. Perucca Em, Richens A. Antiepileptic drugs: Clinical aspects. In: Richen and Marks, Editors. Therapeutic drug monitoring. Edinburgh: Churchill Livingstone ;1981.p.320-44.
7. Renolds EH, Trimble MR. Adverse neuropsychiatric effects of anticonvulsant drugs. Drugs 1985; 29:570-81.
8. Alldrege BK. Seizure Disorders. In: Herfindal ET, Gourley DR. editors. Textbook of therapeuties drug and disease management. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2000.p. 1107-37.
9. Long PW. Phenytoin: Drug monograph. In: Internet mental health. [Online]1995-2008. [cited: 2008 Mar 15]. Available from: URL: http://www.mentalhealth.com/drug/p30-d05.html
10. Adrian MB. Drug interactions that matter. The pharmaceutical Journal 1999; 262 (7035):325-27.
11. Gram L, Bentsen KD, Parnas J, Flachs H. Controlled trials in epilepsy: A review. Epilepsia 1982; 23:491-519.
12. Tartara A, Galimberti CA, Manni R, Parietti L, Zucca C, Baasch H, et al. Differential effects of valproic acid and enzyme-inducing anticonvulsants on nimodipine pharmacokinetics in epileptic patients. Br J clin Pharmacol 1991; 32:335–40.
13. Phospholipid derivatives of valproic acid and mixtures there of. In: Patient Storm. [Online]. US Patent Issued on 2001 Nov 6. [cited: 2008 Mar 3]. Available from: URL:http://www.patentstorm.us/patents/6313106.html
14. Laboratory corporation of America®. Valproic acid (Depakote®), Serum. [Online]. 2007 [cited: 2008 Mar 5]. Holdings and Lexi-Comp Inc. Available from: URL:http://www.labcorp.com/ datasets/labcorp/html/chapter/mono/td027600.html
15. Holmes GL. Epilepsy and other seiznre disorders. In: Berg BO ed. Primciples of child Neurology. New York: Mc Graw-Hill; 1996. p. 223-84.
16. Glauser, TA & Pippenger CE. Controversies in blood level monitoring: Reexaming its role in the treatment of epilepsy. Epilepsia 2000; 41: S6-S15.