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Der Pharmacia Lettre, 2015, 7 (2):243-250
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Evaluation of therapeutic drug monitoring (TDM) on older antiepileptic medications

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ABSTRACT

The Prospective study was conducted to evaluate the measure of Therapeutic Drug Monitoring (TDM) services on conventional antiepileptic drugs (AEDs) in 160 epileptic patients' data of children and adults with both genders was on AEDs. The study results have shown 66 patients (50.38%), under subtherapeutic range on single AEDs with phenytoin and Na.valproate. In 160 patients, 13 of 98 (13.54%) adult patients received co-medication and 3 of 62 (6.25%) children with co-medications. Overall average (V_d) for carbamazepine in adult and children patients was found to be 78.25L which was higher than V_d for phenytoin (35.12L) and Na.Valproate (11.73L). The overall mean of clearance (Cl) for phenytoin (35.59L/hr) was found to be the highest, followed by Carbamazepine (3.81L/hr) and Na.Valproate (0.40L/hr). Na.Valproate had shown the higher value of $C_{ss}(ave)$, which 71.90mcg/ml, than phenytoin (6.39mcg/ml) and Carbamazepine (4.73mcg/ml), where all these three drugs shown highly significant $P < 0.000$. we recommend to bring the 100% of appropriateness of TDM utilization and optimization of the drug dosage by validating the data using screening checklist by TDM pharmacist in the TDM laboratory and the better clinical outcome can be evaluated only by monitoring the pharmacokinetic parameters for the variations appearing on individual patients.

Key words: Conventional Antiepileptic Drugs, Therapeutic range, Post sampling, Co-medications.

INTRODUCTION

Most widely used anticonvulsants [1] in psychiatric practice are carbamazepine and sodium valproate, which are indicated in the treatment of epilepsy and the treatment and prophylaxis of certain psychiatric disorders. TDM assists in the optimization of anticonvulsant therapy [2]. Investigations of prescription patterns and exposure of AEDs to different patient groups are important regarding drug safety aspects [3]. Conventional AEDs the most common enzyme-inducing medications used, and they interact with a wide variety of medications. Despite many therapeutic advances, refractory epilepsy remains a risk factor for sudden unexpected death casue deleterious effects on individual health [4].

In a study of newly diagnosed epilepsy in Malaysia, localization related epilepsies accounted for 57.6% of cases while the remaining 42.4% were generalized epilepsies. Of the generalized epilepsies, sub-classification was as follows: idiopathic generalized epilepsy 28.5%, juvenile myoclonic epilepsy 5.5%, childhood absence epilepsy 3.6%, West syndrome 3%, Lennox Gastaut syndrome 1.2% and photosensitive epilepsy 0.6% [5]. The most commonly used drugs were valproate and lamotrigine in children, carbamazepine and lamotrigine in adults, and carbamazepine and Phenobarbital in the elderly. TDM of older AEDs is requested in the setting of suspected problems with drug compliance, adverse effects or overdose [6].

The application of pharmacokinetic principles in conjunction with monitoring of plasma drug concentrations has led to major advances in the treatment of epilepsy with antiepileptic drugs [7]. The management of antiepileptic drug (AED) pharmacokinetics remains a challenge in the treatment of patients with epilepsy [8]. Use of conventional antiepileptic drugs during pregnancy has been increased risk of birth defects and since 1990s; options for antiepileptic drug treatment have substantially increased [9].

MATERIALS AND METHODS

This study was determined the utilization of Therapeutic Drug monitoring (TDM) service for one year on conventional anti epileptic drugs among children and adults and have evaluated the optimization of the dosage, the toxic and sub-therapeutic drug exposure in epilepsy drug management, the co-medications in patients with epilepsy was characterized including the pharmacokinetic parameters (V_d , Cl , and C_{ss} (ave) on antiepileptic drugs was evaluated among patients. Conventional Antiepileptic Drugs (AED) was evaluated from TDM related records at TDM department with the assistance of TDM pharmacist, in secondary health care hospital. Prospective analysis of Therapeutic Drug Monitoring (TDM) data of Phenytoin (PHY), Carbamazepine (CBZ) and Sodium Valproate (SV) in approximately 160 Inpatients, in whom TDM requisition on uncontrolled seizures, compliance, non-compliance, suspected toxicity, routine drug therapeutic monitoring and therapeutic confirmation for both gender in age group ranging from 1 year to 75 years.

Patients on monotherapy (Single AEDs) and polytherapy of AEDs were included for this study. The TDM pharmacist collected the blood samples from the patients at morning just 30 minutes before the next dose (trough level concentration). The serum was separated by centrifugation method and analyzed in COBAS INTEGRA (ROCHE) which works on the principle based on antigen-antibody binding by Fluorescence Polarization Immunoassays (FPIA). The patients were further categorized under the valid and invalid (rejected) sampling time. From the valid sampling test, the patients were then divided based on their therapeutic range (TR), sub-therapeutic range (S-TR) and toxic range attained. The test values are compared with the established therapeutic ranges for the conventional AEDs.

The data revealed the information on patients' demographic characteristics such as name, age, gender, ethnicity, actual body weight, height, resident address and BMI, information about patients' medical history, chief complaint, diagnosis, history of illness, duration and frequency of epilepsy, medication and its dosage prescribed and co-medications prescribed with AEDs, and information about pharmacokinetic parameters such as V_d , Cl , and C_{ss} (ave). The co-medications together with the AEDs for each patient who had undergone drug monitoring were analyzed.

Epileptic children aged one to 17 years and adult patients aged 18 to 75 years of both genders over a period of one year who are receiving monotherapy or polytherapy from the older antiepileptic drugs (Carbamazepine, Phenytoin, and Sodium Valproate) and who had confident diagnosis of epilepsy were included in this study where neonates below one year and geriatric epileptic patients above 75 years and epileptic patients who were not received the older AEDs was excluded. The patients undergone treatment with vagal nerve stimulation, had device implanted more than 30 days prior to enrollment, who has taken an investigational drug within the previous 30 days or abusing alcohol and/or other substances were also excluded from the objective of the study.

Ethical consideration: This research was approved by the National Medical Research Register (NMRR), NMRR-13-1349-14922 under the Declaration of Helsinki. All the information was collected with the permission of the director, chief pharmacist and supervision of the concern TDM pharmacist of the hospital.

Statistical analysis: Pharmacokinetic data of the epileptic patients and those who were under the categories of sub-therapeutic, therapeutic and toxic range based on the age (adult or children), gender and ethnicity was analysed using statistical package for the Social Sciences SPSS Version 20.0. Prevalence values with their confidence intervals were calculated; means and standard deviation were calculated.

RESULTS

Statistical results of the patient demographics based on gender shows 47% male and 53% female. Based on race, Malay epileptic patients contribute to the highest percentage with 65% followed by Indian and Chinese with 23.12% and 11.88% respectively.

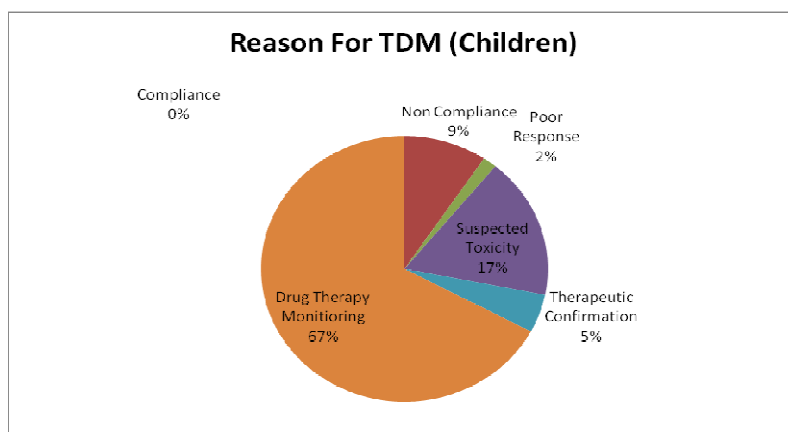
Statistical results showed the reason for the TDM (**Table 1.1**) The reason for TDM were divided into another 5 more categories, with non compliance 9.38% of epileptic children and 15.36% of epileptic adult. Based on the poor response, epileptic children shows higher percentage that is 1.56% and no adults fall under this category. Suspected toxicity, it shows 17.19% epileptic children and 8.33% epileptic adults. With therapeutic confirmation, it shows 4.69% of epileptic children and 4.17% of adult epileptic patients. On the other hand, the drug therapy monitoring, epileptic children shown 67.19% and adult epileptic shows 66.67%.

The total valid samples for the AED concentration were found to be 159/160 (99.4%) and the invalid or rejected sample was found to be 1(0.6%) which has fallen under post sampling.

Table:1.1 Reason for the TDM

Appropriateness of TDM Utilization on AEDs				
Reason For TDM	Children		Adult	
	Number	Percentage	Number	Percentage
Compliance	0	0.00%	5	5.21%
Non Compliance	6	9.38%	15	15.63%
Poor Response	1	1.56%	0	0.00%
Suspected Toxicity	11	17.19%	8	8.33%
Therapeutic Confirmation	3	4.69%	4	4.17%
Drug Therapy Monitoring	43	67.19%	64	66.67%

Figure 1.1: Reason for TDM Distribution in Children & Adult



(**Table 1.2**) shows the monotherapy and polytherapy AEDs distribution based on statistical data, there were 17(10.6%) of the patient was taking carbamazepine, 48(30%) of the patients having phenytoin alone, and 66(41.3%) of the patients was under sodium valproate. As the combination AEDs, one patient was treated with (carbamazepine+phenytoin+sodium valproate), 13(8.1%) of the patients was taking the combination AEDs (carbamazepine+sodium valproate) and there are 15 patients having combination AEDs (phenytoin+ sodium valproate).

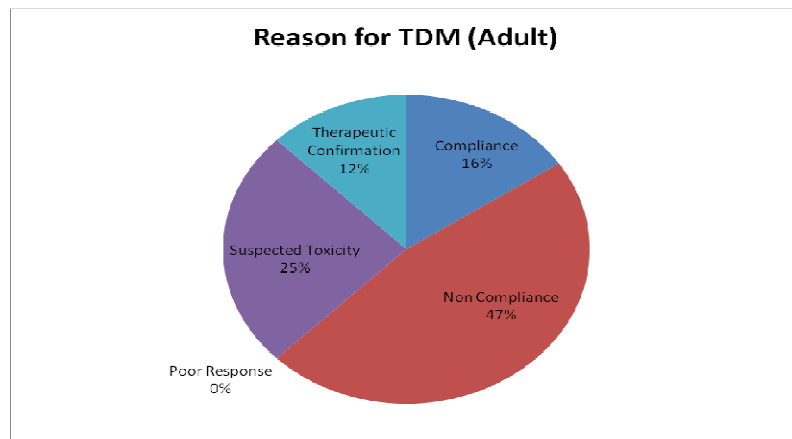


Figure:1.2 Monotherapy and polytherapy AEDs distribution

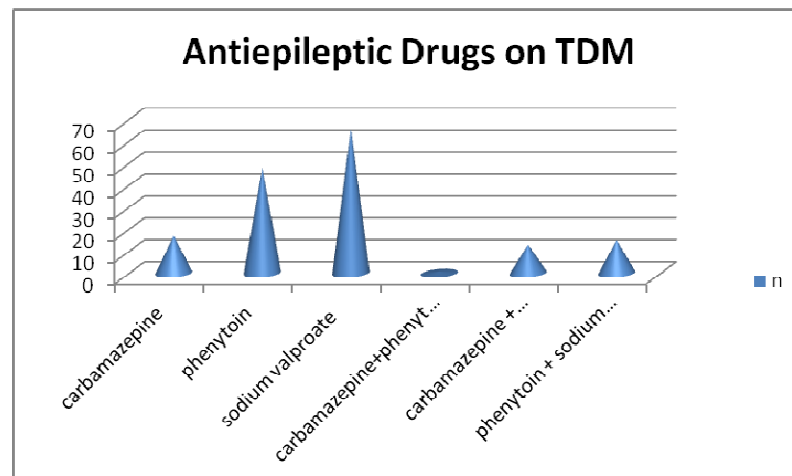


Figure:1.3 Antiepileptic Drug Serum Concentration on single AEDs

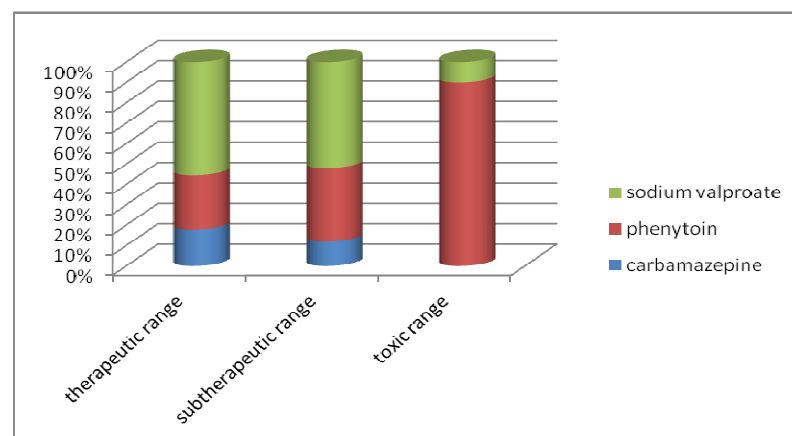


Figure 1.4 Antiepileptic Drug Serum Concentration on polytherapy

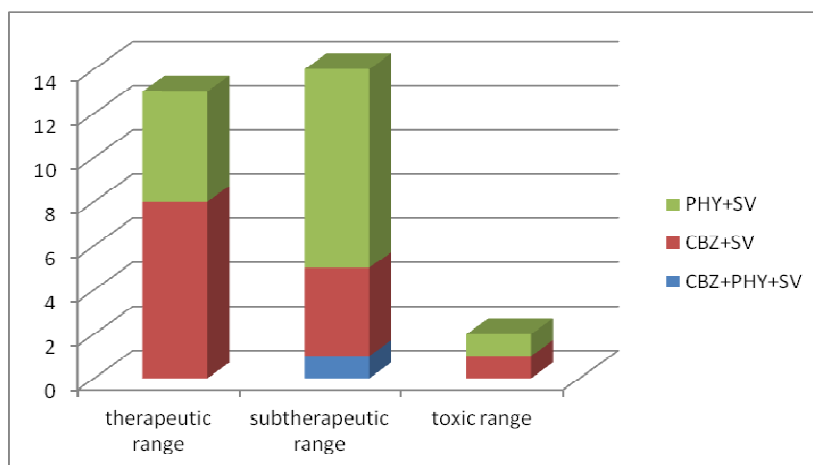


Figure: 1.5 Co-mediations of AEDs Distribution of the Epileptic Patients

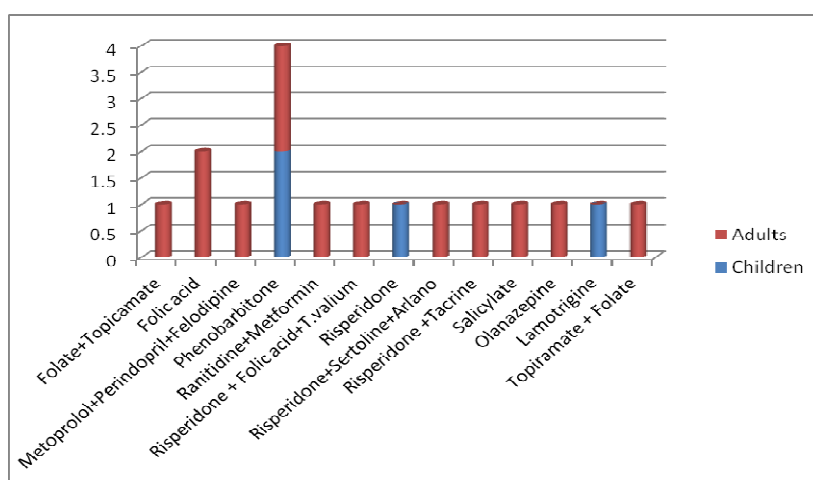


Table 2.0 Pharmacokinetic Parameter Analysis for AEDs

Pharmaco kinetic Parameters	One Way T- test Analysis											
	Phenytoin				Carbamazepine				Sodium valproate			
	n	Mean	Standard Deviation	P-values	n	Mean	Standard Deviation	P-values	n	Mean	Standard Deviation	P-values
Vd	47	35.1270	16.160	P<0.000	17	78.2518	25.7469	P<0.000	66	11.7302	6.5198	P<0.000
Cl	47	35.5906	51.624	P<0.000	17	3.8078	1.35810	P<0.000	66	0.3976	0.3380	P<0.000
Css (ave)	47	6.3926	6.677	P<0.000	17	4.7340	2.29687	P<0.000	66	71.9008	49.1341	P<0.000

(Table 1.3) shown those patients on single AEDs took carbamazepine, there are 8(6.1%) of the patients' AEDs serum concentration within the therapeutic ranges, 9 (6.87%) of the patients' AEDs serum concentration in subtherapeutic ranges and none of them having the AEDs serum concentration in toxic ranges. Those patients under phenytoin, there are 12 (9.16%) of the patients' AEDs serum concentration within the therapeutic ranges, 27(20.61%), in sub therapeutic ranges and 9(6.87%), in toxic ranges. Those patients took sodium valproate, there are 25 (19.08%), within the therapeutic ranges, 39 (29.77%) of the patients', in subtherapeutic ranges and 1(0.76%) in toxic ranges.

(Table 1.4) shown patients on polytherapy of AEDs where, 1 (3.45%) patient was in the subtherapeutic ranges with combination therapy (Carbamazepine+Phenytoin+ Sodium valproate). There were 8 (27.58%) under (Carbamazepine + Sodium valproate) who had the serum AEDs concentration within the therapeutic ranges. Only 4

(13.79%) of the patients took the AEDs combination (Carbamazepine + Sodium valproate) who had the serum AEDs concentration within the subtherapeutic ranges. One 1(3.45%) of the patients took the AEDs combination (Carbamazepine + Sodium valproate) who had the serum AEDs concentration within the toxic ranges. There were 5 (17.24%) of the patients took the AEDs combination (Phenytoin + Sodium valproate) who had the serum AEDs concentration within the therapeutic ranges. Total 9 (31.03%) of the patients took the AEDs combination (Phenytoin + Sodium valproate) who had the serum AEDs concentration within the subtherapeutic ranges. Where one 1 (3.45%) of the patient on AEDs combination (Phenytoin + Sodium valproate) who had the serum AEDs concentration within the toxic ranges.

(Table 1.5) summarizes that among 160 patients, 13 (13.54%) adult patients received co-medication and 3 (6.25%) children were found to be on co-medications.

DISCUSSION

Studies performed locally in Malaysia [10] have been reported improvement in therapeutic concentration achieved and the number of physicians prescribing (Aishah Hamzah and Ab Fatah Ab Rahman 2008).

Optimization of AED dosage on the patients, the monitoring of AED concentration in serum is necessary for the optimal drug therapy of seizures, because the therapeutic and toxic effects of these drugs are better related to serum concentration than to administered dosage. There was no significance difference in epileptic patients with respect to gender for the treatment in Hospital Sultan Abdul Halim. A similar study was conducted, Epilepsy in South East Asia, 1997. The survey showed no significant in the rates among males and females, with significant lower rates in Malays compared to Chinese and Indians. Whereas in recent report of 165 newly diagnosed epilepsy from the University of Malaya Medical Centre, the racial composition were Chinese (36%), Malay (29%), and Indian (35%), thus showing no predisposition to epilepsy among the three racial groups which is contraindicated with our study.

For appropriateness of TDM services, our study shown the epileptic adult patients with more compliance compared to epileptic children patients. On the other hand, mostly TDM was utilized for the drug therapy monitoring. Study conducted by Nadia Affolter et.al, 2003 was the same as our study where out of 139 (23%, 95% CI: 20-27%) levels assessed as having an inappropriate indication, the majority (77%) were performed for routine monitoring.

Based on sampling error and sampling time, 1 out of 160 samples was rejected due to error in sampling time in which the blood sample was taken which increase the appropriateness of TDM utilization. A similar study have been conducted by Irshaid YM 2004 which showed that sampling times were provided in 45% and were considered appropriate in 25.2% of the request forms. The indications for therapeutic drug-monitoring were considered appropriate in 28.6% of the request forms, and only 19.2% of these were appropriately sampled. Only 37.9% of all samples were drawn at steady-state [11].

Monotherapy & Polytherapy AEDs on TDM Based on the monotherapy and polytherapy AEDs, there was more percentage in the patients taking monotherapy AEDs compared to polytherapy AEDs. A similar study was conducted by the Lena K.A.Raty et.al, 2003. The studies showed that patients treated with a combination of two AEDs more often had a poor epilepsy control compared with those on monotherapy. Medication free patients did not have significantly higher frequency of seizures than patients on AEDs. These findings can be explained by the fact that treatment reflects the intractability of the epilepsy [12].

AEDs Ranges on TDM The study results have shown 66 patients (50.38%), have an increased number of subtherapeutic ranges on single AEDs with phenytoin and Valproic Acid. In another similar study conducted by Shakya G, Malla S, Shakya KN and Shrestha, a total of 88 patients from 417 (21.10%) were under sub therapeutic range [13]. A total of 10 patients (7.53%) attained toxic range with single AEDs such as phenytoin and Valproic acid. In a similar study conducted by Shakya G et.al, 2008 a total of 52 of 417 patients (12.47%) achieved toxic range. This may be due to the inappropriate dosage and non-compliance. Therefore addition or deletion of other AEDs with dose adjustments may bring the therapeutic range rather falling under sub therapeutic and toxic range [14].

Co-medications in Patients with Epilepsy Among 160 patients, 13 of 98 (13.54%) adult patients received co-medication and 3 of 62 (6.25%) children were found to be on co-medications. There were no drug interactions for

sodium valproate as it is devoid of enzyme inducing properties. For phenytoin administration with phenobarbitone, there is potentiation of anticonvulsant activity. On the other hand, 2 adults were receiving folic acid and the other 2 adults were receiving phenobarbitone together with AEDs respectively. 9 other adults took co-mediations which were folate and topiramate, metoprolol and perindopril, felodipine, ranitidine and metformin, risperidone, folic acid and T.valium, risperidone and tacrine, salicylate, olanzapine, topiramate and folate. This is due to other underlying disease that patients having apart from epilepsy. All are under therapeutic range except for 2 patients under sub-therapeutic range of which one is taking phenytoin with risperidone and another taking carbamazepine with ranitidine. Phenytoin medicine may only speed up how quickly the liver processes risperidone and not otherwise [15]. Ranitidine also has no effect on carbamazepine level [16]. The sub-therapeutic levels must have been caused by some other unknown factors like for example alcohol abuse.

Pharmacokinetic Parameters of AEDs (Table.2.0) More or less, most of the drugs may display pharmacokinetic variations that cause some degree of difficulty in accurate dosing. This problem is more prominent (and most of the times clinically significant) for drugs with a narrow therapeutic window and non-linear pharmacokinetic like Phenytoin, carbamazepine and sodium valproate.

Overall average Volume of Distribution (Vd) for Carbamazepine in adult and children patients was found to be 78.25L which is higher than Vd for Phenytoin (35.12L) and Sodium Valproate (11.73L). Assuming complete absorption of carbamazepine (high bioavailability), the apparent volume of distribution range was 1.4L/kg. Carbamazepine is bound to serum proteins to the extent of 70 to 80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in the plasma (20 to 30%). A similar study was conducted by Ebrahim Salehifar et.al, 2009. This studies showed there were positive correlations between the dose (and also adjusted dose) with Cpss, Vd and CL in whole patients analysis and demonstrated only half of our patients had the steady-state concentrations within the therapeutic range, i.e. 10-20 mg/L, where 25% had lower and the remaining had upper concentrations [17]. Pharmacokinetic drug interactions must be carefully considered when multidrug therapies are prescribed [18].

Sodium Valproate had shown the higher value of C_{ss} (ave), which 71.90mcg/ml, than Phenytoin (6.39mcg/ml) and Carbamazepine (4.73mcg/ml), suggesting that the regimen of Sodium Valproate per day was more frequent than the other 2 AEDs (Phenytoin and Carbamazepine). CBZ clearance rates have been found to be relatively higher in paediatric patients compared to adults in a study conducted by a Hasnah Ibrahim et.al, 2008. It showed that that younger child may have a higher metabolic capacity for CBZ until they reach adulthood. Studies involving children or groups of patients spanning a wide range of age groups have shown that CBZ clearance significantly correlates with age and weight. Our study focused on both adults and children so the overall mean of clearance (Cl) for Phenytoin (35.59L/hr) was the highest, followed by Carbamazepine (3.81L/hr) and Sodium Valproate (0.40L/hr) suggesting that the rate of hepatic metabolism of Sodium Valproate was the fastest among the two other AEDs. While some patients might be well controlled with plasma concentrations well below the therapeutic range, others might require a higher than therapeutic range plasma concentrations without demonstrating unacceptable adverse effects [19].

CONCLUSION

TDM of older AEDs can still be of some value in the management of patients with epilepsy mainly if indicated for therapeutic noncompliance, exploring sub-therapeutic concentrations and toxicity which might aid in subsequent clinical decision.

First-generation AEDs generally have significant inter-individual variability in their pharmacokinetics (absorption, distribution, metabolism, and excretion) and low therapeutic indices [20].

On the other hand, the most common polytherapy of AEDs had been reported subtherapeutic or slightly therapeutic due to drug-drug interaction. For example, enzyme-inducing AEDs such as carbamazepine and phenytoin can increase the metabolism of sodium valproate and thus, increasing the clearance of sodium valproate which causes a reduction in serum sodium valproate concentration. Most of the patients taking co-medication to treat their underlying diseases like diabetes, hypertension and bipolar depression. However, some of the drugs were taken in adjunct to the treatment to enhance the action of the antiepileptic drugs. The examples of drugs taken in as an adjunct to antiepileptic drugs are phenobarbitone and topiramate.

There were a few limitations in this study that some patients' data records seemed to be unclear and incomplete which did not specify the type of seizures while others did not state clearly the duration and frequency of convulsion. Furthermore, there was no data about the relationship between the response of patients toward AEDs therapy and therapeutic range stated in the patients' medical related records.

Based on this hospital prospective evaluation study there is a immediate need to bring the 100% of appropriateness of TDM utilization and optimization of the drug dosage by validating the data using screening checklist by TDM pharmacist in the TDM laboratory. We recommend that the better clinical outcome can be evaluated only by monitoring the pharmacokinetic parameters for the variations appearing on individual patients, so that the overutilization or under-utilization or optimum TDM utilization service given to the patients can be analyzed and better patient outcomes can be maximized.

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