

**THERAPEUTIC DRUG MONITORING OF ANTIEPILEPTIC DRUGS IN
MARMARA UNIVERSITY HOSPITAL: A THREE-YEAR FOLLOW-UP**

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Summary

TDM is a useful approach for individualizing and optimizing pharmacotherapies. TDM aims optimization of the clinical outcome by managing medication regimen. TDM has been practiced in Turkey since 1980s, and it began in the early 1990s in the Department of Pharmacology and Clinical Pharmacology at Marmara University, Istanbul, Turkey. The position of antiepileptic drugs out of all TDM data between January 01, 2001 and December 31, 2003 were demonstrated. The serum drug levels were measured by fluorescence polarization immune assay and enzyme multiplied immunoassay. Total of 6534 antiepileptic TDM tests were performed for 4011 patients of both sexes. Carbamazepine (n=2221) was the most requested antiepileptic test. Valproic acid (n=1939), phenobarbital (n=1240), and phenytoin (n=1134) were others. Most of the analyses, were within therapeutic ranges (60.7%, n=3968), whereas 30.9% (n=2017) subtherapeutic and 8.4% (n=549) above-therapeutic levels were measured. Most of the results of carbamazepine (76.1%), valproic acid (55.3%), and phenobarbital (75.0%) analyses were within therapeutic ranges, whereas most of the results of phenytoin analyses were subtherapeutic (61.2%). These results show that except for phenytoin, most of the TDM analyses were within therapeutic ranges. This data also reveal extra information about the attitude of physicians regarding TDM of antiepileptic drugs.

Key Words: Antiepileptic Drugs, Therapeutic Drug Monitoring (TDM), Serum Drug Level, Follow up.

List of Abbreviations:

TDM; Therapeutic Drug Monitoring
FPIA; Fluorescence Polarization Immunoassay
EMIT; enzyme multiplied immunotechnique
SEM; Standard Error of Mean

Introduction

Therapeutic drug monitoring is a useful approach for individualizing drug doses (1). Individualizing a patient's drug therapy to obtain the optimum balance between therapeutic efficacy and the occurrence of adverse events is one of the main goals for physicians. However, achieving this goal is not always straightforward, as it is often complicated by intra- and interpatient variability in both pharmacokinetic and pharmacodynamic parameters (2). The observation of inadequate or over dosing has highlighted the importance of measuring drug concentrations in plasma or other body fluids for a more effective patient care. In the early 1960s, new analytic techniques became available, allowing the measurement of low drug concentrations present in biological fluids during drug treatment. These techniques offer the opportunity to reduce the pharmacokinetic variability by controlling drug therapy based on concentrations in the body rather than dose alone. This process became known as therapeutic drug monitoring (TDM) (3, 4).

By its nature, TDM is primarily applicable for medications that possesses narrow therapeutic indices and for agents that demonstrate a good correlation between serum concentrations and pharmacologic effect (5). The rationale for TDM is based on the principle that the intensity of the pharmacological effects of many drugs correlates better with its serum concentration than the dosage (5). TDM aims to optimize the patient's clinical outcome by managing their medication regimen through the guidance of plasma drug concentration levels (3, 4). TDM serves as a useful venue for agents producing a quantal dose-response, such as those used in treating epilepsy where the therapeutic benefit expected from antiepileptics work on an all or none rule (5, 6). The rational pharmacotherapy should be organized in a way that the disease is effectively controlled or cured with no or minimal adverse effects. For achieving this therapeutic goal, TDM is of special interest in monitoring the failure of the conventional drug therapy, patient compliance and suspected intoxication. TDM is also used for the detection of possible drug interactions (7-9) and the age related pharmacokinetic differences of various antiepileptic drugs (10, 11).

TDM of various agents has been practiced in Turkey, predominantly at university hospitals for the last two decades (12). TDM practice began in the early 1990s, in the Department of Pharmacology and Clinical Pharmacology at Marmara University and in 1996 a TDM Unit was established at University Hospital Central Clinical Laboratory (13).

The primary aim of this retrospective study was to audit the requests made for the analysis of four antiepileptic drugs which are carbamazepine (CBZ), phenobarbital (PB), phenytoin (PT), and valproic acid (VA) performed at the TDM Unit of Marmara University Hospital. The secondary aim was to evaluate the relationship between drug concentrations that were reported as sub-therapeutic, therapeutic and or over-therapeutic for each sex over the study period.

Methods

Study Design

This descriptive, cross-sectional and retrospective study was performed by using the data collected from the TDM Unit of Marmara University Hospital, between January 01, 2001 and December 31, 2003, where the results of analytical measurements of antiepileptic drugs and patient information charts of the TDM Unit were evaluated. The following descriptions of methods are of those used in the present study and those currently used.

TDM Unit, Blood Sampling and Analytic Assays

Marmara University Hospital is both a referral and a teaching hospital with a 400-bed capacity. TDM requests come from various hospitals and other medical institutions but mainly from university outpatient and inpatient clinics. TDM analysis results are given as report printouts to patients or nurses. In emergency cases, the patients' physicians are called as well. All of the assays are uploaded to the hospital computer network of hospital for physicians' quick access to the results.

An antiepileptic drug TDM service is provided for carbamazepine, valproic acid, phenobarbital and phenytoin as well as for some chemotherapeutics, immunosuppressants, and cardiac drugs, and some toxic substances are being assayed. Immunosuppressant drug assays are performed in whole blood samples and for all other measurements serum samples are used. At our TDM unit, only the total concentration of the drugs in the samples is measured.

Fluorescence polarization immunoassay FPIA were performed on TDx, IMx and AxSYM systems, (Abbott Laboratories, IL, USA) and enzyme multiplied immunoassay EMIT were performed on Emit 2000 Viva system, (Dade Behring, IL, USA). Standard calibrations were regularly performed, and internal quality control samples regarding low, medium and high levels were also assayed regularly and when necessary. Additionally external quality assays were performed at regular intervals as a part of inter-hospital validation and quality assessment procedure.

Generally, patients are admitted to the laboratory in the morning without having taken their morning doses; this corresponds to the pre-dose period. If they consume their morning doses before admission to the laboratory the patients are warned, and the sampling is performed the following day. The blood samples are collected arbitrarily in emergency situations, but the time of sampling in respect to the timing of the last dose is always recorded for interpretation of the results.

Patient Information Sheets and Data Collection

Pharmacologists or pharmacology assistants whom are all medical doctors and work at the TDM unit perform a face-to-face interview and fill out the patient-information charts for all patients admitted to the unit. The information of the in-patients was supplied by the responsible physicians in the clinics. The patient information chart contains 3 questions; i) the patient characteristics i.e. age, sex, current diagnosed disease(s), presence of hypoproteinemia, renal or hepatic dysfunction, ii) detailed history of pharmacotherapy (drug, trade name, formulation, daily dose, dose interval, time of the last dose, concurrent use of other drugs, duration and efficacy of ongoing pharmacotherapy e.g. occurrence of seizures for antiepileptics), iii) appropriateness of sampling (blood sampling time, protocol number of the patient, sample identity number). All the analytical and the patient data are stored in a computerized database at the unit. The therapeutic ranges of the antiepileptic drugs that are accepted for our hospital are listed in Table 1 (3).

Table.1 Therapeutic ranges of the antiepileptics for therapeutic drug monitoring (Evans and Oellerich, 1984).

Drug	Therapeutic ranges	
Carbamazepine (CBZ)	4-11 µg/ml	17-47 µmol/L
Phenobarbital (PB)	10-40 µg/ml	40-170 µmol/L
Phenytoin (PT)	10-20 µg/ml	40-80 µmol/L
Valproic acid (VA)	50-100 µg/ml	350-700 µmol/L

Statistical analysis

Data are expressed as mean ± SEM or percentage. Chi-square test was performed to identify possible range for each drug. The level of statistical significance was accepted as P < 0.05.

Results

A total number of 9628 tests were performed within the 36-month period, 6534 were for antiepileptic drugs and 3094 tests were for other drugs (Fig. 1). The number of patients admitted to the TDM unit of Marmara University Hospital for antiepileptic drug monitoring was 4011 and a total of 6534 antiepileptic TDM analyses were performed for these patients. Of the patients, 51.5% (n=2065) were female and 48.5 % (n=1946) were male (Table 2).

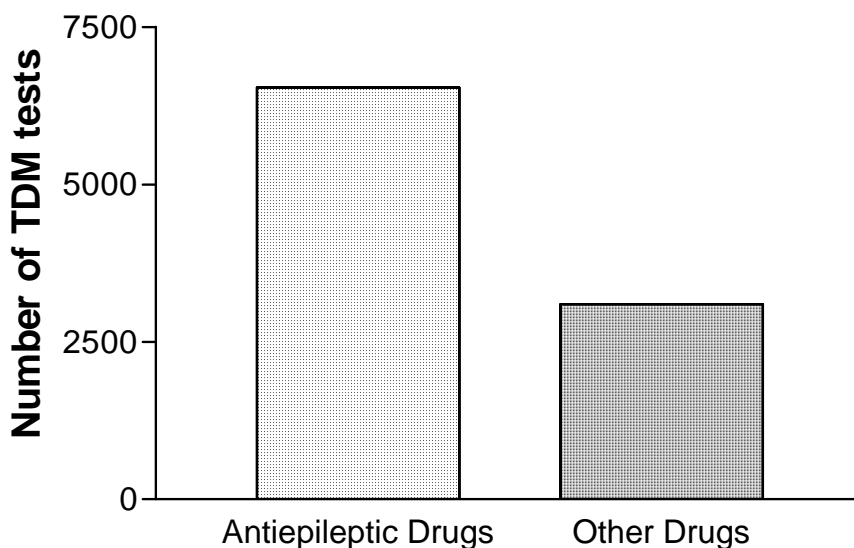


Figure 1: The total number of therapeutic drug monitoring analyses performed in Marmara University hospital within 36-month period between January 1 2001 and December 31 2003

Table 2: The distribution of the therapeutic drug monitoring performed for the antiepileptics in respect to patient sex and years.

Drug	2001		2002		2003		Total	
	Female	Male	Female	Male	Female	Male	Female	Male
Carbamazepine	258	209	252	219	247	240	757	668
Phenobarbital	192	160	209	176	121	130	522	466
Phenytoin	109	100	106	126	173	228	388	454
Valproic acid	87	75	90	102	221	181	398	358
Total	646	544	657	623	762	779	2065	1946

CBZ (n=2221) was the most requested antiepileptic drug from our TDM unit, VA (n=1939), PB (n=1240), and PT (n=1134) were the other antiepileptic drugs monitored within the 36-month period (Fig. 2).

Of all antiepileptic TDM analyses, 60.7% were within therapeutic ranges (n=3968), whereas 30.9% and 8.4% were sub-therapeutic (n=2017) and above-therapeutic (n=549) levels respectively (Fig. 2).

Most of the results of CBZ (76.1%), VA (55.3%), and PB (75.0%) analyses were within therapeutic ranges, whereas most of the results of PT analyses were sub-therapeutic (61.2%) (Fig. 2).

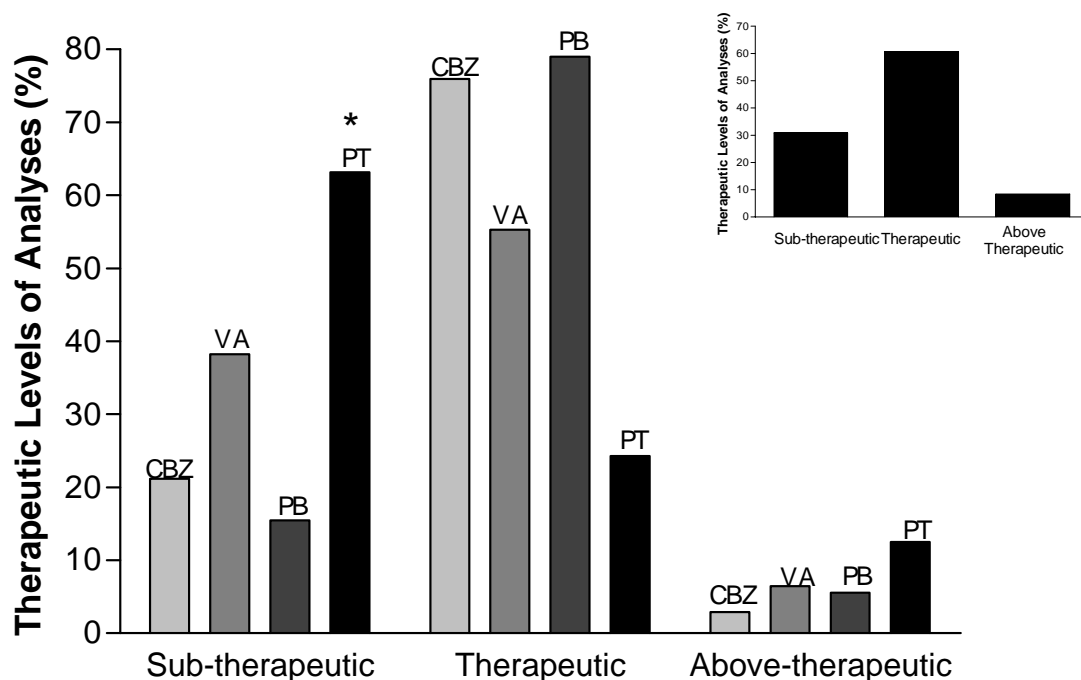


Figure 2: The distribution of therapeutic drug monitoring analyses of four antiepileptic drugs in respect to therapeutic ranges classified as sub-therapeutic, therapeutic or above-therapeutic level. The inset figure shows the ranges of the pooled data. CBZ: carbamazepine; VPA: valproic acid; PHB: Phenobarbital; PHT: phenytoin.

*, p<0.05 (Compared to the sub-therapeutic levels of other antiepileptic drugs; Chi-square test).

Table 3: The arithmetic means of therapeutic drug monitoring assays of four antiepileptic drugs (µg/ml) in respect to sex of the patients.

Ranges	Carbamazepine		Valproic acid		Phenobarbital		Phenytoin	
	Female	Male	Female	Male	Female	Male	Female	Male
Sub-therapeutic	2.2 ± 0.1	2.3 ± 0.1	31.8 ± 0.8	31.9 ± 0.8	5.1 ± 0.3	5.6 ± 0.4	4.7 ± 0.2	4.6 ± 0.2
Therapeutic	6.7 ± 0.1	6.7 ± 0.1	71.8 ± 0.5	69.0 ± 0.6	21.5 ± 0.4	22.5 ± 0.3	14.2 ± 0.3	13.9 ± 0.2
Above-therapeutic	15.8 ± 0.9	14.2 ± 1.1	123.1 ± 5.2	115.4 ± 2.0	53.4 ± 2.0	53.6 ± 1.4	27.7 ± 0.9	32.1 ± 1.5

Levels measured above-therapeutic concentrations were 4.4, 7.6, 11.5 and 14.4% of total CBZ, VA, PB and PT analyses, respectively (Fig. 2).

Of CBZ analyses, 19.6% (n=435) were sub-therapeutic, whereas 76.1% (n=1689), and 4.4% (n=97) were within therapeutic and above-therapeutic ranges, respectively (Fig. 2). Of VA analyses 37.1% (n=720) were sub-therapeutic, whereas 55.3% (n=1072), and 7.6% (n=147) were within therapeutic and above-therapeutic ranges, respectively (Fig. 2). Of PB analyses 13.6% (n=168) were sub-therapeutic, whereas 75.0% (n=930), and 11.5% (n=142) were within therapeutic and above-therapeutic ranges, respectively (Fig. 2). Of PT analyses 61.2% (n=694) were sub-therapeutic, 24.4% (n=277) and 14.4% (n=163) were within therapeutic and above-therapeutic ranges, respectively (Fig. 2).

Differences in the mean sub-therapeutic, therapeutic and above-therapeutic plasma concentrations for each sex are given in table 3. No difference in the number of analyses were classified as sub-therapeutic, therapeutic and above-therapeutic was detected for the years 2001, 2002 and 2003 (Table 4).

Table 4: The number of therapeutic drug monitoring tests of four antiepileptic drugs performed in the years 2001, 2002 and 2003 in Marmara University Hospital in respect to therapeutic ranges.

<i>Ranges</i>	All AEDs			Carbamazepine			Valproic acid			Phenobarbital			Phenytoin		
	2001	2002	2003	2001	2002	2003	2001	2002	2003	2001	2002	2003	2001	2002	2003
Sub-therapeutic	700	668	649	175	138	122	241	242	237	58	51	59	226	237	231
Therapeutic	1267	1290	1411	553	570	566	360	339	373	274	283	373	80	98	99
Above-therapeutic	114	142	293	12	31	54	39	43	65	16	23	103	47	45	71
Total	2081	2100	2353	740	739	742	640	624	675	348	357	535	353	380	401

Table 5: The distribution of the therapeutic drug monitoring assay requests of four antiepileptic drugs in the years 2001, 2002 and 2003 from different departments.

<i>Departments</i>	Carbamazepine			Valproic acid			Phenobarbital			Phenytoin		
	2001	2002	2003	2001	2002	2003	2001	2002	2003	2001	2002	2003
Neurology and Psychiatry	59.5	53.5	40.2	59.8	52.9	46.2	32.8	23.0	18.5	18.7	17.6	17.2
Neurosurgery	11.2	11.2	9.3	2.5	3.2	4.9	11.5	12.0	6.2	38.2	34.7	39.6
Pediatrics	12.2	11.2	12.1	21.1	20.4	24.0	37.1	39.5	52.9	21.8	21.6	11.4
Emergency	3.8	7.9	6.7	3.1	6.1	3.7	5.2	9.0	4.1	4.8	9.7	4.0
Other departments	4.6	6.2	4.7	1.9	3.5	2.1	6.6	9.0	3.6	5.7	10.8	6.0
Other hospitals	8.8	10.0	27.0	11.6	13.9	19.1	6.9	7.6	14.8	10.8	5.5	21.9
Total	100	100	100	100	100	100	100	100	100	100	100	100

The percentage of test requests from the various departments for antiepileptic drugs were also determined (Table 5). Most of the requests came from the departments of neurology and psychiatry, neurosurgery and pediatrics (Table 5). CBZ and VA test requests came from mostly from the neurology and the psychiatry departments, whereas most of the PT requests were from the neurosurgery department (Fig 3). In addition, PB was mostly requested (52.9% in the year 2003) by the pediatrics department (Table 5). The trend in the number of PB TDM tests was tended to increase in years 2001, 2002 and 2003.

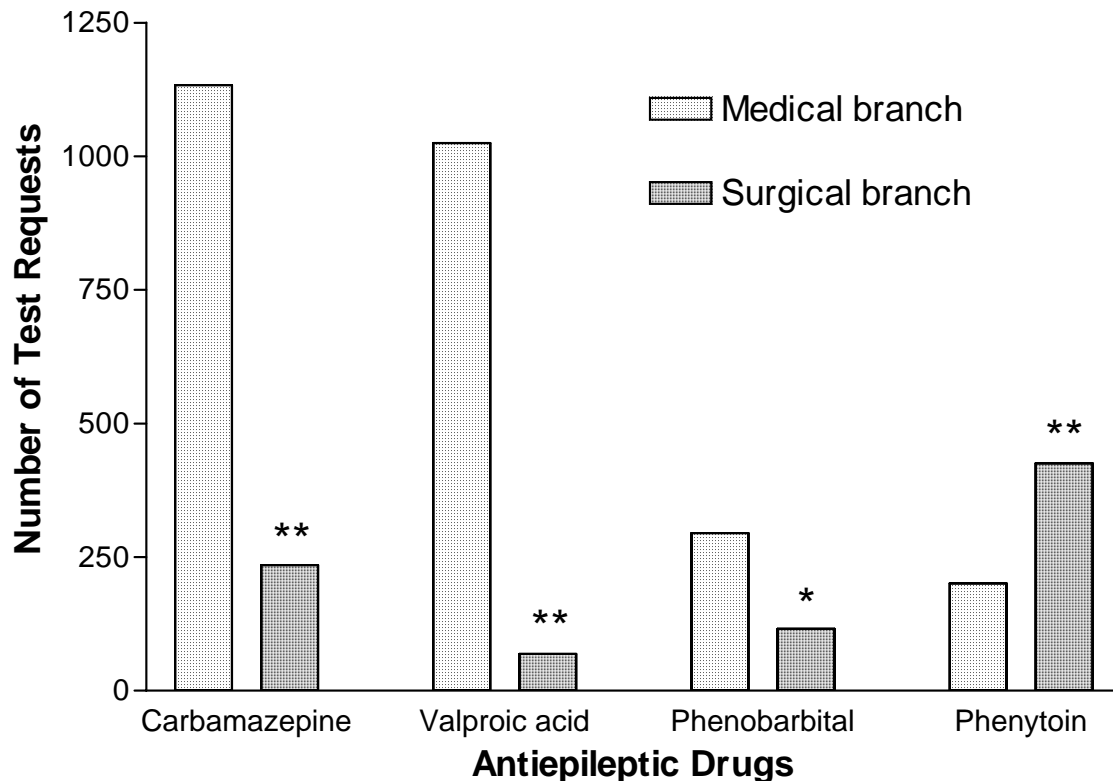


Figure 3: The comparison of the number of antiepileptic test requests from neurology and & psychiatry and neurosurgery departments.

*, $p < 0.05$, **, $p < 0.001$ (compared with the corresponding medical or surgical departments of the neurological sciences).

Discussion

TDM is commonly used to optimize drug treatment in various diseases by monitoring drug concentrations. Antiepileptic drug level determination is a substantial part of all drug concentration measurements in the TDM units.

After its establishment, our TDM unit developed quickly and reached approximately 4000 tests per year. The place of TDM for the older antiepileptic drugs was well established in Marmara University Hospital and for the 36-month period, which was between January 01, 2001 and December 31, 2003, this number totaled 6534 tests.

The most requested TDM tests in our hospital were for antiepileptic drugs. Many newer antiepileptic drugs including oxcarbazepine, levetiracetam, lamotrigine have been marketed in

Turkey in recent years so the serum drug level monitoring of newer antiepileptic drugs should be carried out (14).

Although PT was previously reported to be the most requested drug for TDM analyses (15), our data, in agreement with other sources (16) showed that CBZ test was the most frequently performed TDM analyses. Thus, although CBZ is the most frequently requested TDM test and may be the most prescribed antiepileptic drug in our hospital, but it must also be kept in mind that CBZ is also used for other indications such as trigeminal neuralgia and bipolar mood disorders other than epilepsy (17, 18).

Although the majority of test results for CBZ, VA, and PB were within the therapeutic ranges, most of the PT results were found to be sub-therapeutic. The most logical explanation for this finding may be the fear of the clinicians to cause iatrogenic PT toxicity. However the sub-therapeutic levels may not always indicate ineffective treatment. In some patients effective outcome may be achieved at sub-therapeutic levels and most of the PT test requests were from neurosurgery clinics of Marmara University and other hospitals. Furthermore, most of the results of the PT tests requested from neurosurgery wards were sub-therapeutic. Although the long term use of PT is not recommended (19), PT has been prescribed extensively in neurosurgery for the prevention of possible post traumatic epilepsy. We also recognized that most of the patients were using PT for 2 years after their surgery. Surprisingly, a few patients were still under PT treatment 10 years following the surgery (data not shown) even though those patients were not diagnosed as being epileptic. Furthermore, statistical analysis yielded that, the proportion of the results reported to be above-therapeutic levels for PT were significantly higher than those of the other drugs. Although the clinicians were in the habit of escalating the PT dose carefully with the fear of inducing the toxicity, our data once more show that above-therapeutic levels can be reached frequently, suggesting that adjusting PT dose is not an easy procedure. However, interpretations only made by measuring the total concentration rather than the free fraction may be misleading in certain situations. Good seizures control may be obtained at total concentrations in the sub-therapeutic range if the free levels of PT are within the free level therapeutic range. For this reason, not only the total PT levels, but also free fraction of PT should be measured to optimize clinical outcome. Unfortunately, no laboratory or TDM center in Turkey measures free PT level is available and this problem may need to be addressed in the near future. New antiepileptic drugs should also be included to the recent TDM menu in a near future to help certain patients with particular epileptic disorders (20, 21). It is also as much important to minimize the interlaboratory differences by using external quality control assessments (22).

Unlike the other antiepileptic drugs studied (15, 16), a significantly higher proportion of PT analyses were within the sub-therapeutic range.

Statistical analyses failed to demonstrate any sex differences between the mean sub-therapeutic, therapeutic and above-therapeutic concentrations for each drug studied.

TDM is a process that begins with the acceptance of the samples and continues with the interview of the patients for their medical history, chemical assays and finally interpretation of the results. During this process, lack of information about the patients' medical history and the drug regimens will compromise the effectiveness of the TDM service (13, 23). In order to minimize these problems, the clinician and the patients should be more informed about the TDM.

Our results show that most of the TDM analyses were within therapeutic ranges. On the other hand, sub-therapeutic plasma drug levels were not infrequent. Although sub-therapeutic antiepileptic drug levels might be acceptable if the clinical response is satisfactory, the clinician needs to be supported by a competent TDM facility. The importance of the communication and collaboration between the clinician and the clinical pharmacologist is essential for the well being of the patients.

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