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ORIGINAL ARTICLE

Therapeutic Drug Monitoring Characteristics in a City Hospital for a Year

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SUMMARY

Background: **Therapeutic drug monitoring (TDM) involves the measurement of drug concentrations in serum, plasma, whole blood, or other biologic fluids. This study focused on evaluating the TDM requests of a city hospital over a period of one year, retrospectively.**
Methods: **The study retrospectively analyzed TDM requests for carbamazepine, cyclosporine-A, digoxin (DIGOX), lithium (LITH), methotrexate (MTX), phenitoin, tacrolimus, and valproic acid (VALP) from June 1, 2022, to June 1, 2023. Parameters such as the age and the gender of patients, the requesting departments, the measurement results, and the turnaround time (TAT) were assessed. Drug concentrations below the reference values were classified as subtherapeutic, whereas concentrations above the reference values were considered supratherapeutic.**
Results: **In total, 10,913 drug concentration measurement records were analyzed. The gender distribution was 51.6% male and 48.4% female. Pediatric samples comprised 6.2% and elderly samples 8.6% of the total. Notably, DIGOX, LITH, and VALP levels showed a significant correlation with age (p = < 0.0001, p = < 0.0001, and p = 0.0002, respectively). TAT was maintained at 360 minutes (6 hours) for all tests.**
Conclusions: **The study found significant correlations between age and DIGOX, LITH, and VALP levels. TDM plays a critical role in the elderly population, necessitating careful management of these drugs.**
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INTRODUCTION

Therapeutic drug monitoring (TDM) involves the measurement of drug concentrations in various biological fluids, including serum, plasma, whole blood, and others, as a critical component of clinical pharmacology [1, 2]. For a drug to be suitable for TDM, it must have a narrow therapeutic range, notable pharmacokinetic variability, a clear relationship between plasma concentrations and clinical effects, a defined target therapeutic reference range, and the availability of a cost-effective drug assay. TDM applications include optimizing dosing (post-dose adjustment, evaluating sufficient loading, etc.), monitoring therapy (assessing compliance, identi-

fying undertreatment or therapy failure), and managing toxicity. Crucially, TDM encompasses not only the measurement of drug concentrations but also their clinical interpretation, necessitating an understanding of pharmacokinetics, appropriate sampling times, drug background, and the patient's clinical status [2].

The timing of sample collection is pivotal because drug concentration fluctuates throughout the dosing interval. Ideally, samples should be collected just before the administration of the next dose. The interpretation of TDM results requires information on the timing of sample collection, the timing of the last dose, the dosing regimen, and the indication for TDM [3-5].

Common measurement methodologies for drugs include chromatographic techniques (high-performance liquid chromatography (HPLC), liquid chromatography-tandem mass spectrometry (LC-MS/MS)), immunoassays, and biosensors [1]. Most assays quantify total drug concentration, both bound and unbound, though it is the free drug that is pharmacologically active [2].

This study retrospectively evaluated TDM requests for carbamazepine (CARB), cyclosporine-A (CYC-A), digoxin (DIGOX), lithium (LITH), methotrexate (MTX), phenytoin (PHT), valproic acid (VALP), and tacrolimus (TACRO) in a city hospital over a 1-year period.

MATERIALS AND METHODS

We conducted a retrospective analysis of the TDM requests recorded between June 1, 2022, and June 1, 2023. The study included data from both inpatients and outpatients. Patient demographics, including age and gender, were extracted from the hospital records. Age groups were categorized as pediatric (0 - 18 years), adult (18 - 65 years), and elderly (> 65 years). Parameters such as the requesting department, measurement results, and turnaround time (TAT) of the tests were evaluated. Therapeutic ranges were established based on the laboratory reference values, with exceptions for MTX, CYC-A, and TACRO, for which no single reference value exists due to a variability that is influenced by daily conditions and concomitant medications. Concentrations below reference values were classified as subtherapeutic, while those above were considered supratherapeutic. TAT was measured from the reception of the sample to the dispatch of the report. Ethical approval for this study was granted by the Ethics Committee of the Prof. Dr. Cemil Taşcioğlu City Hospital (issue number: 2023/205).

Analytical testing was performed using Roche Cobas 8000 c702 (Mannheim, Germany) for CARB, DIGOX, LITH, PHE, and VALP; Roche Cobas 6000 c501 (Mannheim, Germany) was used for MTX; and Roche Cobas 8000 e801 (Mannheim, Germany) was used for CYC-A and TACRO.

Descriptive statistics were calculated for age, sex, drug levels, and TAT. Spearman's rank correlation coefficients (confidence interval: 99%) were calculated for age and each drug. Statistical analyses were conducted using GraphPad Prism software version 8.02 (USA).

RESULTS

Between June 1, 2022, and June 1, 2023, 10,913 drug concentration measurements were recorded. The monitored drugs included CARB, CYC-A, DIGOX, LITH, PHE, MTX, TACRO, and VALP. VALP was the most frequently requested drug for TDM, accounting for 42.3% of the requests, whereas MTX was the least frequently requested at 0.5%. The gender distribution of the patients was 51.6% male and 48.4% female (Table 1).

In terms of age distribution, 6.2% of the samples were from pediatric patients, 8.6% were from the elderly, and the remaining 85.1% were from the adult age group. When considering the laboratory cut-off values, 56.5% of the samples were within the therapeutic level range, 37.2% were subtherapeutic, and 6.1% were supratherapeutic. Gender ratios and mean ± standard deviation values of the test results were calculated for all tests (Table 1).

Upon reevaluating the age and drug concentration groups, significant differences were observed. DIGOX, LITH, and VALP showed significant correlations with age ($p = < 0.0001$, $p = < 0.0001$, and $p = 0.0002$, respectively). The elderly age group exhibited a higher ratio of supratherapeutic levels of DIGOX. PHE showed a higher ratio of subtherapeutic levels across all age groups (Figure 1 - 4).

The highest number of TDM requests originated from the neurology department (51.72% for PHE, 67.41% for CARB, and 30.45% for VALP), nephrology (41.74% for TACRO and 52.69% for CYC-A), psychiatry (50.11% for LITH), internal medicine (35.05% for DIGOX), and hematology (63.29% for MTX) (Figure 5). The percentages of the tests according to age are also shown in Figure 6.

TAT was measured for all tests, with all results being delivered within 360 minutes (6 hours). Median times were recorded as 237, 358, 265, 253, 317, 153, 278, and 280 minutes for CARB, CYC-A, DGX, LITH, PHT, MTX, TACRO, and VALP, respectively (Table 2).

DISCUSSION

This retrospective study assessed 10,913 blood samples for TDM in a city hospital equipped with 1,100 beds, 166 intensive care units, and 28 operating rooms. The drugs evaluated included CARB, CYC-A, DIGOX, LITH, PHT, MTX, TACRO, and VALP, with the most frequently monitored being VALP, LITH, and CARB (Table 1).

Yamantürk et al., study from the same region, analyzed 7,759 blood samples for TDM, focusing on drugs such as CARB, VALP, PHE, DIGOX, phenobarbital, theo-

Table 1. Therapeutic drug monitoring details by age, gender, plasma drug level (mean ± SD), reference range, and dispersion of classification based on the reference range.

Drug name	Age min - max (mean ± SD)	Female (%)	Male (%)	Drug concentration (mean ± SD) (therapeutic reference range)	Subthera-peutic level	Therapeutic level	Suprathera-peutic level	Total number
CARB	7 months - 91 (39.39 ± 16.04)	48.20%	51.70%	8.22 ± 3.74 (4 - 12 µg/mL *)	9.33%	77.43%	13.22%	1,925
DIGOX	10 months - 96 (70.38 ± 19.38)	69.17%	30.82%	1.41 ± 1.22 (0.6 - 1.2 µg/L *)	22.68%	30.58%	46.74%	292
LITH	11 - 85 (42.8 ± 13.53)	60.30%	39.60%	0.43 ± 0.21 (0.42 - 0.83 mg/dL *)	40.38%	56.58%	3.04%	2,597
PHE	10 months - 90 (40.15 ± 25.43)	52.10%	47.90%	6.21 ± 6.65 (10 - 20 µg/mL *)	80.93%	13.87%	5.20%	173
VALP	1 - 92 (39.21 ± 16.38)	42.60%	57.30%	51.55 ± 26.48 (50 - 100 µg/mL *)	33.01%	64.47%	2.52%	4,623
CYC-A	3 - 80 (44.14 ± 19.01)	34.50%	65.40%	Median: 49.00 25%: 31.00 75%: 61.00 (100 - 400 ng/mL) (28)				336
MTX	5 - 85 (57.45 ± 2.33)	49.10%	50.90%	Median: 61.00 25%: 44.00 75%: 69.00				55
TACRO	3 - 88 (40.42 ± 18.88)	41.50%	58.40%	Median: 6.25 25%: 4.32 75%: 8.34 (5 - 20 µg/L) (28, 29)				912

*** - the therapeutic reference ranges were taken from the kit package insert.**

Table 2. TAT periods for the tests.

Test	Mean minutes	Median minutes	Target minutes	Performance %
CARB	237	165	360	84.75
CYC-A	358	196	360	75.66
DIGOX	265	178	360	79.60
LITH	258	188	360	81.14
PHT	317	218	360	72.16
MTX	153	116	360	92.31
TACRO	278	152	360	77.78
VALP	280	185	360	81.21

phylline, and salicylate. Their findings indicated a lower frequency of pediatric samples within the therapeutic range [6]. Ozunal et al. assessed TDM in a tertiary university hospital, examining drugs such as CARB, DIGOX, LITH, and VALP. Their analysis showed that 72.8% of the samples were within the therapeutic level range, 21.9% were subtherapeutic, and 5.3% were toxic, with a notably high ratio of toxic levels in the pediatric group for the four drugs (54.5%) [7].

In our study, 56.5% of the samples were within the therapeutic concentration range, 37.2% were subtherapeutic, and 6.1% were supratherapeutic. Because the therapeutic reference ranges are only valid for defined blood collection time points, a reason for concentrations outside the therapeutic reference range can be an incorrect blood sample time. The timing of sample collection is very important, because drug concentration fluctuates throughout the dosing interval.

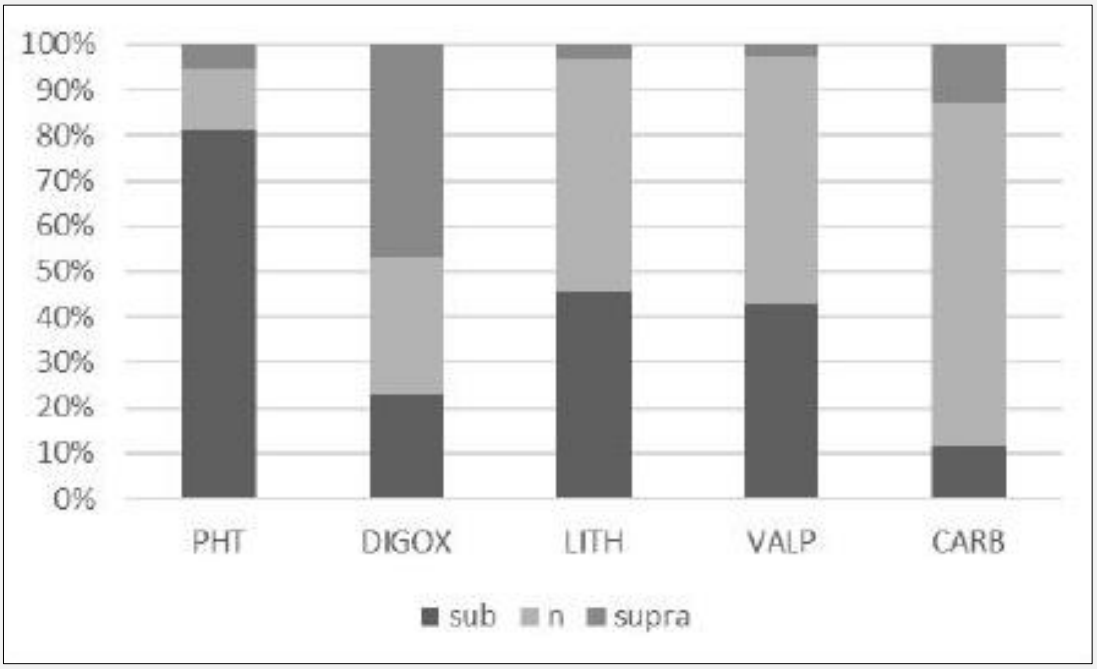

Figure 1. Percentage of drug concentrations within (n), below (sub), and above (supra) the therapeutic reference range.

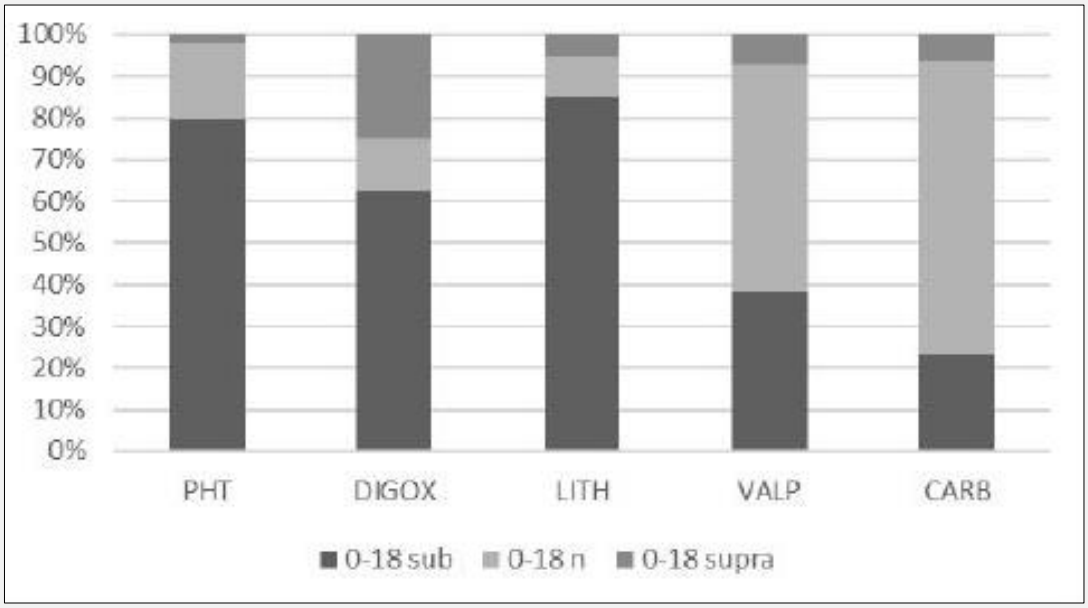

Figure 2. Percentage of drug concentrations within (0 - 18 n), below (0 - 18 sub), and above (0 - 18 supra) the therapeutic reference range for the pediatric group.

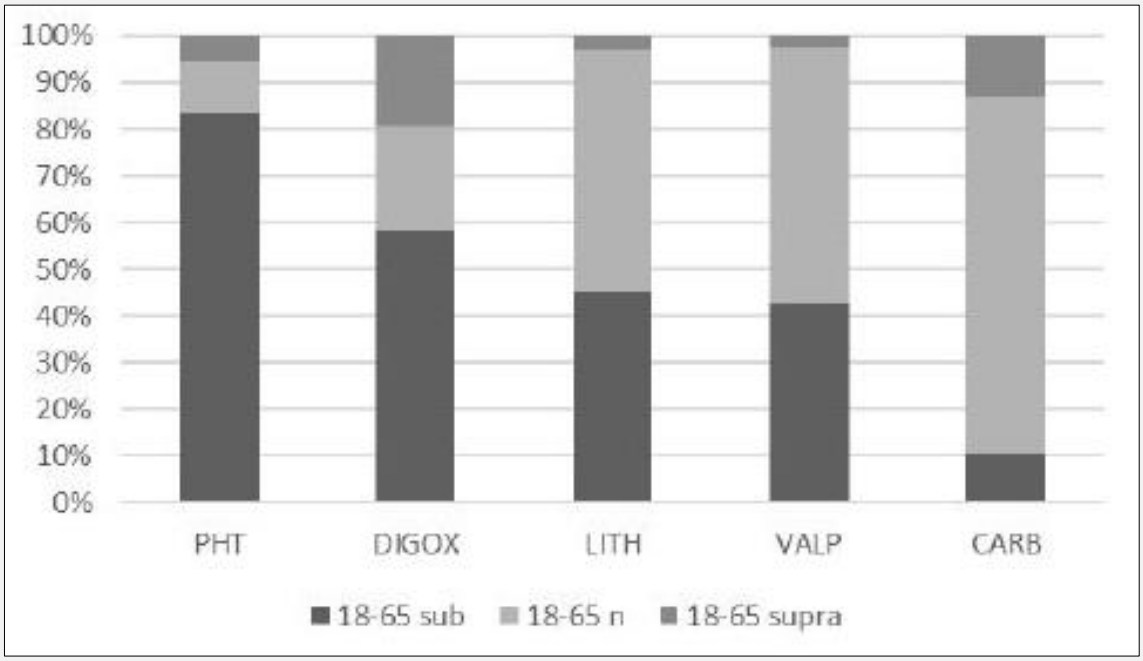

Figure 3. Percentage of drug concentrations within (18 - 65 n), below (18 - 65 sub), and above (18 - 65 supra) the therapeutic reference range for the adult group.

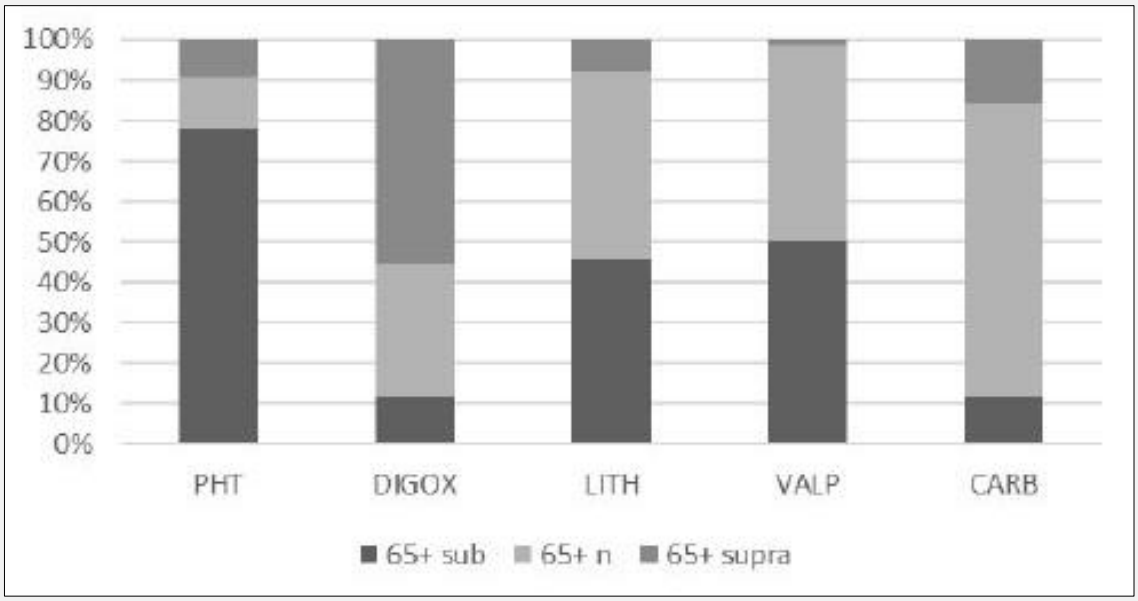

Figure 4. Percentage of drug concentrations within (65+ n), below (65+ sub), and above (65+ supra) the therapeutic reference range for the elderly group.

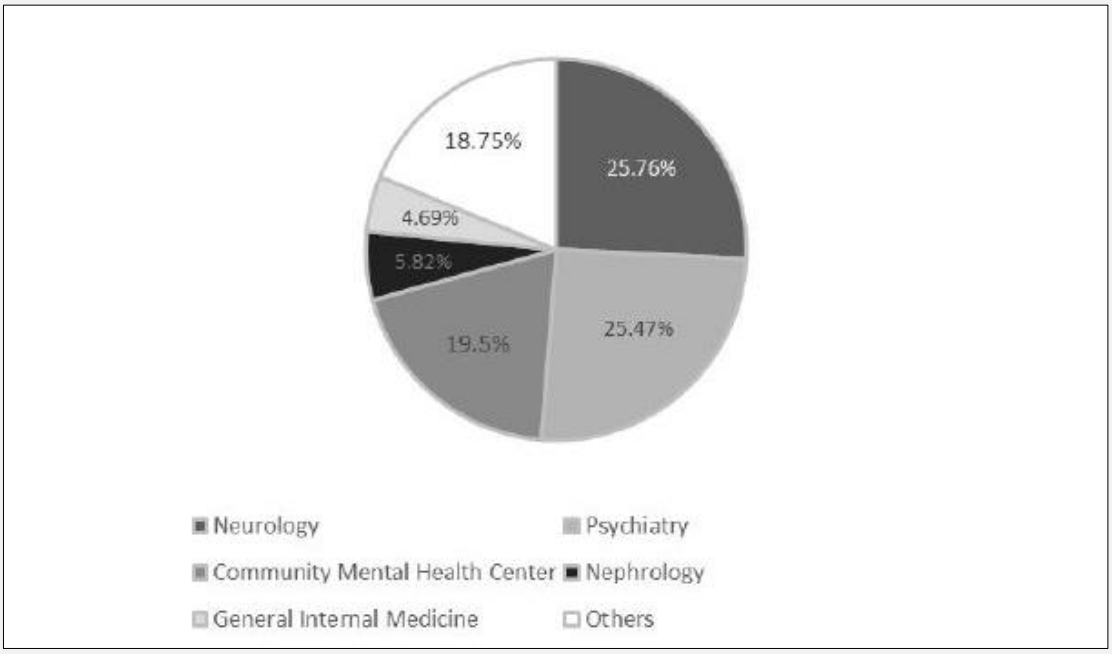

Figure 5. The requesting department for the tests.

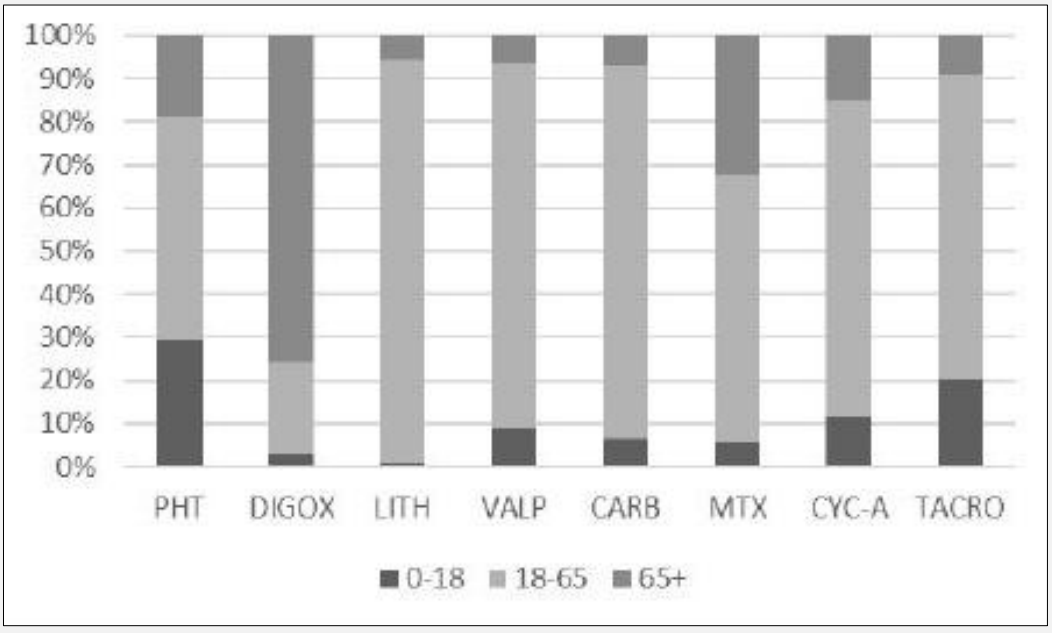

Figure 6. Percentage of tests according to age.

CARB, a first-generation antiepileptic drug, is vital for the management of neuropsychiatric diseases [8]. Our data showed the highest CARB requests from neurology (67.41%) and psychiatry (12%). Using the kinetic interaction of microparticles in solution (KIMS) method with Roche Cobas 8000 c702 (Mannheim, Germany), we found 77.43% of CARB samples were within the therapeutic range. This aligns with Grzesk et al., who reported 71% of patients within the therapeutic range, using fluorescence polarization immunoassay [9]. Eroğlu et al. analyzed TDM results for antiepileptic drugs over a period of five years, finding 60% of CARB results within the therapeutic reference range, 16% supratherapeutic, and 24% subtherapeutic [10].

DIGOX is commonly used for treating congestive heart failure and atrial fibrillation, particularly in the elderly. Elderly patients are at a higher risk for DIGOX toxicity because of age-related renal function decline and reduced DIGOX distribution volume. Comorbidities such as cardiovascular and chronic obstructive pulmonary diseases, common in the elderly, increase susceptibility to DIGOX toxicity. Co-administration with quinidine and calcium channel blockers can also elevate DIGOX serum levels [11,12]. Our study corroborates these findings, with the elderly group showing a higher ratio of supratherapeutic levels. DIGOX analysis was performed using the KIMS method with a Roche Cobas 8000 c702. The primary requesting departments included internal medicine (35.1%), intensive care (22%), and cardiology (11%). Ylmaz et al.'s evaluation of DIGOX monitoring in the elderly found 46.6% of the levels therapeutic, 29.2% subtherapeutic, and 24.2% toxic, with the highest toxicity in patients over 85 years, resonating with our findings [13].

LITH is extensively used for treating bipolar disorder. Because of its narrow therapeutic range, TDM for LITH is the standard practice. Guidelines recommend measuring its concentration both at initiation and during maintenance therapy [14]. Analysis was performed using the photometric method with a Roche Cobas 8000 c702 (Mannheim, Germany). In our study, most requests came from psychiatry (50.1%), community mental health centers (34.5%), and internal medicine (5.6%). We observed that 56.58% of the LITH samples fell within the therapeutic range, and a significant correlation with age was found ($p = < 0.0001$). Ratanajamit et al. reported that 44.6% of the serum LITH levels in 83 samples were outside the therapeutic range [15]. Age-related factors, such as comorbid conditions and concurrent medications, can affect LITH pharmacokinetics in the elderly, necessitating lower doses to achieve similar serum concentrations as in younger adults, likely due to reduced distribution volume and renal clearance [16].

PHE is predominantly used for epilepsy treatment. Increased plasma concentrations or toxic levels of PHE are linked to genetic polymorphisms, particularly in CYP2C9*3, and are significantly associated with severe cutaneous adverse reactions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [17]. In our study, PHE showed a higher ratio of subtherapeutic drug levels across all age groups. Analysis was conducted using the KIMS method in Roche Cobas 8000 c702 (Mannheim, Germany), with neurology (51.72%) and intensive care (20%) as the primary requesting departments. Mekloy et al. found 33.24% of the PHE levels were subtherapeutic and 15.41% were supratherapeutic in their TDM analysis [18]. Srivastava et al. reported that in children, 23.5% of the serum total PHE levels were therapeutic, 31.3% subtherapeutic, and 49% supratherapeutic [19].

VALP is widely used in adults for treating convulsions, migraines, and bipolar disorders [20]. In our study, the analysis was performed using the enzyme-multiplied immunoassay technique in Roche Cobas 8000 c702 (Mannheim, Germany). The main requesting departments were neurology (30.45%), psychiatry (27.8%), and community mental health centers (24.9%). We found 64.47% of the VALP samples within the therapeutic range. Shaikh et al. reported that 58% of the VALP levels were within therapeutic range in a study of 206 plasma samples from patients with epilepsy [21]. Perucca et al. and Bryson et al. found no significant change in the distribution volume or elimination half-life between elderly and younger patients [22,23].

MTX serves as an antimetabolite in the metabolism of folic acid. It enters the cell and competitively inhibits the enzyme dihydrofolate reductase, thereby hindering the conversion of dihydrofolate to tetrahydrofolate. Tetrahydrofolate is essential for the synthesis of thymidine and purines, which are crucial for DNA synthesis [24]. By blocking tetrahydrofolate synthesis, MTX impedes both cell division and protein synthesis [25]. In our study, MTX represented the least frequent test with only 79 instances (0.5%). The primary departments requesting this test were hematology (63.29%) and internal medicine (22.78%). Drug analysis was conducted using the enzyme-multiplied immunoassay technique (EMIT) with Roche Cobas 6000 c501 (Mannheim, Germany). Kivity et al. investigated serum concentrations of MTX in hospitalized patients and found detectable levels (mean 0.04 ± 0.07; range: 0 - 0.3 µmol/L) in 68% of the cases [26]. However, they observed no significant correlation between MTX concentrations and the severity of neutropenia ($r = -0.36$; $p = 0.18$) or thrombocytopenia ($r = 0.44$; $p = 0.10$). Song et al. suggested maintaining MTX concentrations below 0.1 - 0.2 µmol/L, with the recommendation that TDM can be discontinued once these levels were achieved. Furthermore, they proposed that for children with acute lymphoblastic leukemia, the MTX plasma concentration at the end of a 24-hour infusion should be maintained at 16 - 40 µmol/L [27].

The clinical application of immunosuppressants has significantly improved patient outcomes, with first-year survival rates reaching up to 90% for renal transplants [28]. CYC-A and TAC function as calcineurin inhibitors, impacting lymphocyte proliferation [29]. TDM of

CYC-A and TAC is essential for effective treatment in transplant patients, addressing variable pharmacokinetics, acute infection, dosage adjustments, compliance checks, and long-term therapy continuation. Because of their narrow therapeutic indices, TDM for CYC-A and TAC is crucial to minimize drug toxicity while preventing graft loss and organ rejection. The therapeutic reference range depends on the type of transplant, the time post-transplant, the co-administration of other drugs, and the drug formulation. Wong et al. have outlined targeted whole blood immunosuppressant concentration ranges, specifying 100 - 400 ng/mL for CYC-A and 5 - 20 ng/mL for TACRO, varying with methodology, therapy, and organ type [28]. Dušan et al. reported therapeutic ranges of 50 - 300 µg/L for CYC-A and 5 - 20 µg/L for TACRO [29]. In our study, TACRO and CYC-A were primarily requested by nephrologists, account ing for 41.74% and 52.69% of the requests, respectively. Drug analysis was conducted in whole blood using the electrochemiluminescence immunoassay (ECLIA) method with Roche Cobas 8000 e801 (Mannheim, Germany). The median and percentile values were 49, 25% percentile: 31.00, and 75% percentile: 61.00 ng/mL for CYC-A and 6.25, 25% percentile: 4.32, and 75% percentile: 8.34 ng/mL for TACRO, aligning with the aforementioned studies.

TAT is a key indicator of laboratory service quality and is commonly used to assess laboratory performance [30]. In our study, TAT was measured from the reception of the sample to the dispatch of the report. Ideally, laboratory TAT should be shorter than the dosing interval [2]. In our study, all tests were completed within 360 minutes (6 hours), meeting the recommended durations for therapeutic management. These results are specific to our reference laboratory and may not reflect general availability. Furthermore, it should be mentioned that our laboratory provides a 24-hours/5 days TDM service. Test availability varies among hospitals and cities. Goswami et al. evaluated TAT for both outpatient and hospitalized patients over a year by calculating TAT from phlebotomy to result reporting. They found an average TAT of 5.5 hours for routine inpatient clinical biochemistry samples, whereas outpatient samples had a TAT of 24 hours. The TAT for stat samples was 1 hour [31].

Limitations of our study are the absence of information of collecting time, the asset of concominant drugs and the aim of requesting TDM.

CONCLUSION

The correlation of the DIGOX, LITH, and VALP results with age were evident in our findings. This underlines the critical importance of TDM in elderly patients, where clinicians must be vigilant about the management and the potential toxicity of these drugs. Effective TDM necessitates a multidisciplinary approach, encompassing the entire process from the pre-analytical phase to the final interpretation. TDM is a multifaceted process that includes deciding to request a drug level, handling the biological sample, making the request, conducting laboratory measurements, communicating results, and integrating clinical interpretation and therapeutic management. This process extends far beyond merely measuring drug levels.

For accurate interpretation of drug concentrations, essential information includes the time of the blood sample collection, the dosage regimen (dose, duration, dosage form), the patient demographics (gender, age, concomitant diseases, ethnicity, etc.), the co-medications, the indications for monitoring, the pharmacokinetics, and the therapeutic range of the drug [5]. Integrating these data into electronic request orders could be a practical approach. Promoting teamwork through TDM educational meetings involving patients, nurses, technicians, referring physicians, clinical biochemist specialists, and clinical pharmacologists is crucial. This collaborative approach is now recognized as an indispensable tool for a more effective, patient-centered healthcare [32].

Declaration of Interest:
None.

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