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RESEARCH ARTICLE

EVALUATION OF SERUM DRUG CONCENTRATIONS IN A TERTIARY CARE HOSPITAL: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Serum drug concentration (SDC) is an important parameter used in drug efficacy and treatment follow-up.
Aim: This study aimed to evaluate subtherapeutic, therapeutic and toxic SDCs, SDC measurement requests and demographic specialities (age and sex) for carbamazepine, phenytoin, phenobarbital, lithium and digoxin.
Materials and Methods: This is a cross-sectional study, evaluating the outpatients' and inpatients' SDC data treated at Research and Application Hospital of Afyonkarahisar Health Sciences University between January 1, 2012 and February 28, 2019, and having SDC data. The relations between dependent and independent variables was evaluated with chi-square analysis and Students' T-test. $P<0.05$ was considered statistically significant.
Results: A total of 3735 patients, 8946 admissions (mean: 41.1±26.6 years, 51.3% females) and 10158 SDCs were reviewed. Digoxin SDC was the most common measurement, at a rate of 33.7%. The highest number of SDC measurement was made in 2016 (n=1627). Subtherapeutic SDC rates were high for phenytoin, lithium, and digoxin (69.8%, 39.7%, 35.8%, respectively). Digoxin (16.2%) and phenobarbital (9.8%) were the drugs with the highest rate of toxic SDC. SDC increased for all drugs with increasing age, this was statistically significant for carbamazepine, lithium and digoxin ($P<0.05$). SDC for digoxin was found to be significantly higher in female sex ($P<0.001$).
Conclusion: In this study, subtherapeutic and toxic SDC levels were examined. This study revealed the need for prospective studies evaluating Therapeutic Drug Monitoring (TDM) together with patient- and drug-related factors.

Keywords: therapeutic drug monitoring, serum drug concentration, digoxin, phenobarbital, phenytoin

INTRODUCTION

Measuring drug concentration in blood is a method applied for many years, providing better information than drug dosage in terms of drug efficiency and safety. In this method, which is based on biochemical analysis alone, drug concentrations are interpreted within the specified therapeutic range, regardless of patient related factors.The therapeutic index of a drug is the concentration range between the minimum effective concentration and the minimum toxic concentration of the drug (1). Interpretation involves only subtherapeutic, therapeutic and toxic levels. This information is necessary for the clinician to set the dose of the drug.

Serum drug concentration (SDC) is not measured for each and every drug. Thus, certain drug-related criteria were determined in order to perform a SDC measurement: if the therapeutic range is narrow, if it is ineffective or toxic, when the dosage is changed, if there is a drug-drug interaction, and if it is clinically difficult to observe the effect of the drug (2, 3). SDC has been measured for years for antiepileptic (e.g. phenytoin), antiarrhythmic (e.g. digoxin), antidepressant (e.g. lithium), antibiotic (e.g. vancomycin), antineoplastic (e.g. methotrexate) and immunosuppressive (e.g. cyclosporine) drugs (4,5).

In our country however, SDC measurement started in the 1980s. Studies based on SDC measurements are limited and conducted in tertiary healthcare institutions (6-8). Evaluating merely drug levels was the major limitation of these retrospective studies, where demographic data and SDC measurement requests affecting the drug level were not taken into account.

Our study, carried out between 2012 and 2019 in a tertiary healthcare institution, aimed to evaluate a) the number of SDC measurement requests by different drugs; b) SDC rate at subtherapeutic, therapeutic and toxic levels; and c) the demographic specialities (age and sex) affecting SDC.

MATERIALS AND METHODS

This is a descriptive and cross-sectional study. The study was initiated after the approval Afyonkarahisar Health Sciences University- Non-Interventional Research Ethics Committee (Date: 13.05.2022, Decision No: 2022/309) and was carried out in line with the principles of the Declaration of Helsinki.

The patients with SDC data who applied to AFSU Health Application and Research Center between January 1, 2012 and February 28, 2019 constituted the sample. The date of data collection: February-July 2022. The sample size was calculated as minimum 310 individuals by the Open Epi program, with a deviation of 5% and a confidence level of 95%, in line with the information obtained from previous studies, and accepting the average therapeutic limit as 72% for the antiepileptic serum drug level (6-8). However, the patients sample was not selected by any limitation rule, but all the patients who met the inclusion criteria within the specified date range were included in the study. All the patients of all age ranges, who received outpatient or inpatient treatment at AFSU Application and Research Center, and whose SDC was measured, were included in the study. The SDC ratio (number of tests/number of patients) was calculated. An attempt was made to standardize this ratio by calculating the average number of SDC measurements per patient.

SDCs were measured spectrophotometrically by Cobas 8000 analyzer (Roche) in AFSU Medical Biochemistry Laboratory. Standard calibrations, internal and external quality control tests were regularly performed. Therapeutic ranges were defined as 4-12 µg/ml for carbamazepine, 10-20 µg/ml for phenytoin, 10-30 µg/ml for phenobarbital;

Table 1. Drugs with SDC measurements and demographic characteristics of the patients

Drug	Number of Patients n	Number of Applications n	Number of Tests n	Mean Age (S) Years	Gender	
					Female (%)	Male (%)
Carbamazepine	662	2015	2078	20.3 (16.0)	917 (44.1)	1161 (55.9)
Phenytoin	200	289	321	35.4 (21.5)	128 (39.9)	193 (60.1)
Phenobarbital	339	1036	1112	3.8 (2.5)	498 (44.8)	614 (55.2)
Lithium	585	2759	3220	39.4 (13.7)	1637 (50.8)	1583 (49.2)
Digoxin	1949	2847	3427	67.2 (16.6)	2031 (59.3)	1396 (40.7)
Total	3735	8946	10158	41.1 (26.6)	5211 (51.3)	4947 (48.7)

S: Standart deviation

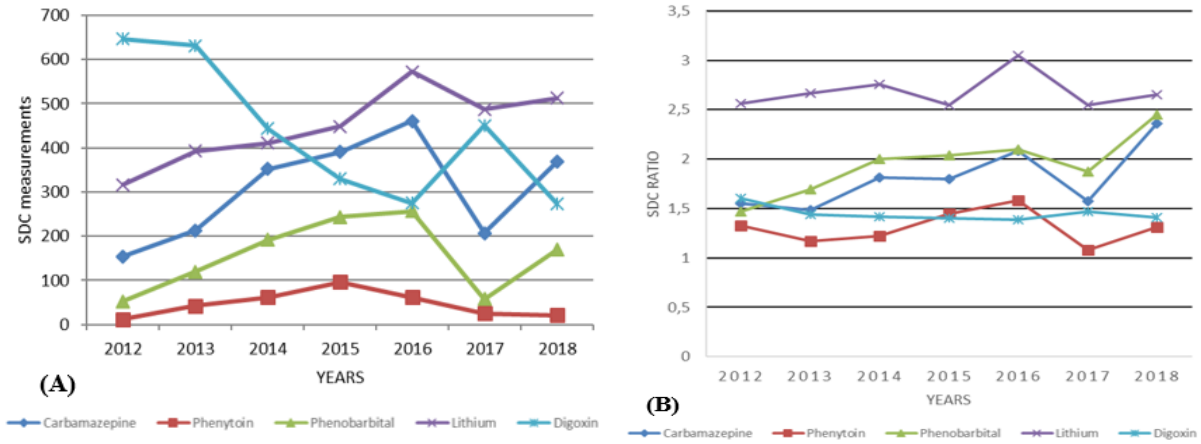

Figure 1. The trend of change serum drug concentration (SDC) measurement numbers and SDC ratio by years. A) SDC measurement numbers. B) SDC ratio: Number of Tests / Number of Patients

0.6-1.2 mmol/l for lithium and 0.6-1.2 ng/ml for digoxin. In line with the literature, 2.0 ng/ml and above was accepted as toxic level for digoxin (9).

Statistical analysis

Descriptive statistical analysis was implemented for the demographic data and laboratory findings of each hospitalization of the patients. Results were presented as number (n), percent (%), mean ± standard deviation (S). In the descriptive statistics by years, there was only 2 months of data for 2019. For this reason, data for 2019 was not presented in the chart.

The relationship between dependent and independent variables was evaluated by chi-square analysis for categorical variables and by Students's t test for the variables indicated by measurement. The median values of the age factor, as an independent variable, were calculated for each drug. Based on these median values, analyses were performed by seperating into two groups. Data were analyzed with the statistical program SPSS-24 (SPSS INC., Chicago, IL, USA). P<0.05 was considered statistically significant.

RESULTS

A total of 10158 SDCs were measured in 3735 patients. The most SDC was measured for digoxin, while the least for phenytoin (Table 1). Mean age of the patients was 41.1±26.6 years and 51.3% were female. The rate of patients under 18 years of age was 24.1%, while the rate of patients aged 65 and over was 25.6%. Mean age of the patients with SDC measured was highest for digoxin (67.2±16.6 years) and lowest for phenobarbital (3.8±2.5 years) (Table 1).

The least number of SDC measurements was performed for phenytoin (3.2%) over eight years and the most for digoxin (33.7%) (Table 1). The second most frequent SDC measurement was for lithium (31.7%). As for the SDC measurements by years, the highest number was in 2016 (n=1627), while the lowest in 2017 (n=1229). The number of SDC measurements for digoxin decreased over the years, and displayed fluctuations after 2016. The number of SDC measurements for phenobarbital and lithium showed an increasing trend over the years, but a substantial drop was determined in 2017. The change in the number of SDC measurements of drugs by years is presented in Figure 1 (A). The SDC ratios showed a similar trend to the SDC measurement numbers. In patients taking lithium, the SDC ratio ranged from 2.55 to 3.05, and it was the drug most frequently requested per patient (Figure 1 (B)). Although digoxin was the drug with the most requests, its SDC ratio was the lowest and the least requested drug per patient.

About three-quarters of the measured SDCs for carbamazepine and phenytoin were detected at the therapeutic level. While 23.7% of the SDC measured for phenytoin was within the therapeutic range, 69.8% was below subtherapeutic level. It was determined that 29.5% of the SDC measured for digoxin was above 1.2 ng/ml, while 16.2% was at the toxic level (>2 ng/ml). Among the drugs with SDC data, the highest toxic level was found for digoxin, followed by

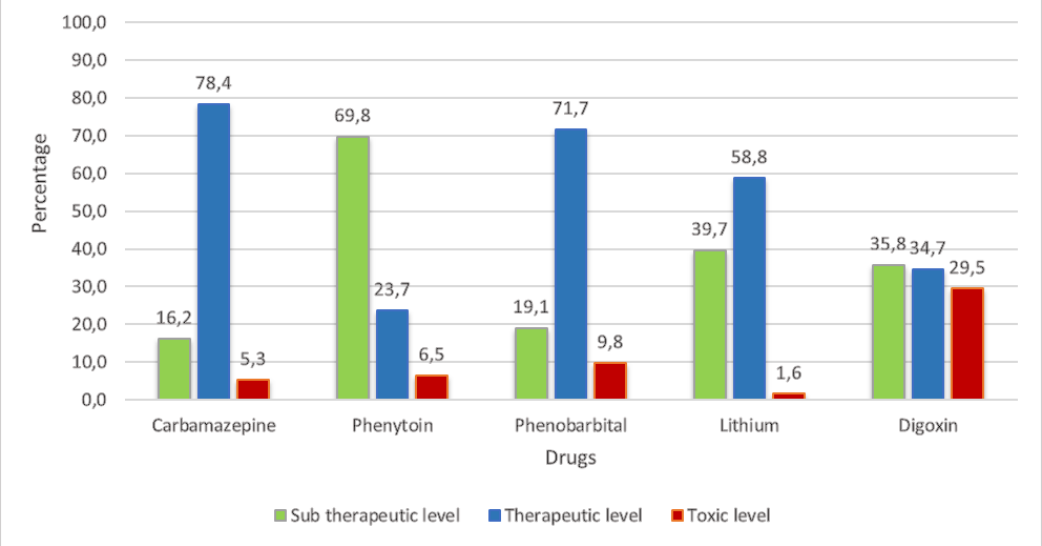

Figure 2. Serum drug concentration (SDC) percentage of subtherapeutic, therapeutic and toxic levels

phenobarbital with a rate of 9.8% (Figure 2). Looking at the rates of toxic levels of digoxin and phenobarbital over the years, we find that they were highest in 2019 (Figure 3).

As for the factors affecting SDC, the concentration was found to increase for all drugs with increasing age, and this was statistically significant for carbamazepine, lithium, and digoxin (Table 2). With respect to sex factor however, SDC was found to be higher in female sex for all drugs except phenobarbital, but there was statistical significance only for digoxin (Table 3).

DISCUSSION

In this study, SDC measurement results of/in a tertiary university hospital, with a capaciy of 655 beds and approximately 450 thousand outpatients per year, are presented retrospectively. The most frequent SDC measurement was for digoxin. The sample size was higher with respect to the similarly designed studies in Turkey, where data were analyzed retrospectively (7, 8). When compared with two different studies evaluating only digoxin SDC, the number of digoxin SDC measurements (n=3427) was higher with respect to the study of Özyiğit et al., and similar to the study of Yılmaz et al. (10, 11). The number of SDC measurements for antiepileptics was less that that of the study by Karaalp et al (12). In our study, the results of all drugs whose SDC was measured were evaluated, were not specific to only one drug group.

The mean age of the patients with SDC measurement was highest for digoxin and lowest for phenobarbital. Digoxin is a drug used in the treatment of heart failure and atrial fibrillation. Determining a high value for the mean age due to the the indication of use, gave out similar results with respect to the other studies in the literature (13, 14). Phenobarbital is an antiepileptic agent that is frequently used in the neonatal and childhood age group (15) . For this reason, in our study, the mean age of the patients with phenobarbital SDC was found to be low, in accordance with the literature (16).

A complex trend was observed in the SDC measurements of these drugs over the years. SDC measurement was more balanced for phenytoin, while it tended to decrease for digoxin and to increase for other drugs. However, in 2016-2017, SDC measurement reversed its trend for the other drugs except phenytoin. The number of SDC measurements was very low, especially in 2017. Just the contrary was observed for digoxin SDC measurement. This may be attributed to the doctor requesting the test. There is no TDM Service in our hospital. Considering the variation in the study results by the physicians requesting SDC measurements, it is apparent that there is a need for more information on TDM and a standardization of the requests of drugs in the clinical unit.

In addition to regular monitoring of serum lithium concentrations because of its very narrow therapeutic range, it is said that more extensive monitoring is needed even when SDC is in the "normal" range. Age, polypharmacy, and morbidities are important factors that accelerate lithium toxicity (17). These differences between the SDC ratios of the drugs

Figure 3. Serum drug concentration percentage of subtherapeutic, therapeutic and toxic levels by years. A) Carbamazepine, B) Phenytoin, C) Phenobarbital, D) Lithium, E) Digoxin.

indicate that the requested department and physicians ordered the test without paying attention to the SDC order indications.

Phenytoin, lithium and digoxin were the drugs with the highest SDC at subtherapeutic level. This rate was about 70% for phenytoin, which was very high. But in a study on TDM of antiepileptic drugs in Turkey (12), this rate was 61%, which was close to the rate we found in our study. However, this rate varied between 35-37% in the studies conducted in several other countries, which was much lower with respect to our study results (18, 19). The accepted therapeutic range for phenytoin SDC may not be valid for all patients. SDC is related to the type and severity of the seizure, and it is not recommended to increase the dose of phenytoin in patients having seizures controlled at a subtherapeutic level (20). However, there is a study reporting subtherapeutic levels of phenytoin in most of the patients with seizures (21). Besides individualization of the dose and SDC, it is also extremely important to assure therapeutic range as much as possible and to consider patients' data when interpreting SDCs (22).

In the study, the SDC for lithium was found at a subtherapeutic level of 40%. Nepal et al. found the SDC rate for lithium as 14% in their study conducted in a tertiary healthcare institution (23). In two other studies with similar research samples, the SDC rate for lithium was found to be 30% and 32%, which were closer to our study results (24,25). Lithium has been used in the treatment of bipolar disorder for many years. In addition to the studies reporting that low-dose lithium treatment can increase constructive behavior while decreasing destructive behavior, providing neuroprotective benefits and causing less suicide and psychosis (26,27), there are also some

Table 2. Comparison of SDC levels between age groups

	Age (n)	Mean (S)	P
Carbamazepine	**15 ≥** (1078)	6.3 (3.1)	***< 0.001***
	15 < (1000)	7.3 (3.2)	
Phenytoin	**36 ≥** (162)	7.5 (6.8)	0.359
	36 < (159)	8.2 (7.0)	
Phenobarbital	**1 ≥** (655)	17.4 (9.6)	0.194
	1 < (457)	18.3 (11.8)	
Lithium	**37 ≥** (1686)	0.59 (0.25)	***<0 .001***
	37 < (1534)	0.64 (0.33)	
Digoxin	**70 ≥** (1723)	0.90 (0.89)	***<0 .001***
	70 < (1704)	1.22 (1.0)	

Age was analyzed by dividing the patients into two groups based on the median value for each drug. Student's t-test was performed. S: Standart deviation

Table 3. Comparison of SDC levels between gender

	Gender (n)	Mean (S)	P
Carbamazepine	**Female** (917)	6.9 (3.3)	0.309
	Male (1161)	6.7 (3.1)	
Phenytoin	**Female** (128)	8.2 (7.6)	0.512
	Male (193)	7.7 (6.5)	
Phenobarbital	**Female** (498)	17.6 (10.6)	0.606
	Male (614)	17.9 (10.5)	
Lithium	**Female** (1637)	0.62 (0.32)	0.744
	Male (1583)	0.61 (0.26)	
Digoxin	**Female** (2031)	1.21 (1.10)	***< 0.001***
	Male (1396)	0.87 (0.90)	

Student's t-test was performed

other studies indicating less adverse effects at low concentrations despite more relapses (28,29). It was also reported that low and high serum lithium concentrations displayed no difference (30). In the light of these information, it was recommended to target SDC for lithium treatment as 0.6-0.75 mmol/l, and as 0.8-1.0 mEq/L for newly diagnosed patients if they can tolerate it (29-31).

Approximately two-thirds of digoxin SDC was detected outside the therapeutic range. The reference range for digoxin was recognised as 0.8-2 ng/ml by the laboratories, for a long time. However, the target SDC in heart failure was suggested as 0.5-0.9 ng/ml for digoxin in advanced analysis of the Digitalis Investigation Group (DIG) study, revealing that mortality was reduced at low SDC (13). Therefore, considering its use for atrial fibrillation too, the lower limit of SDC for digoxin was updated as 0.6-0.7 ng/ml (32). The reason for the high rate of subtherapeutic SDC for digoxin in our study was that low SDC was targeted by considering the guidelines and clinical studies. (32). However, subtherapeutic concentrations below 0.5 ng/ml for digoxin were accepted as '*undetectable SDC*' in the literature, which was determined as 7%, lower than our study results (33). There is no information on the efficacy of digoxin at very low concentrations. For this reason, it should be taken into consideration that subtherapeutic SDC may cause failure in treatment. Among the medicines, digoxin displayed the highest toxic CDC levels, with the rates of 30% (>1.2 ng/ml) and 16% (>2 ng/ml). This was followed by phenobarbital at a rate of 10%. In the studies examining the relationship between Digoxin SDC and mortality, SDC was determined above 1.2 ng/ml at a rate of 23.7%-36.7%, consistent with our results (33-35). Considering the toxic level >2 ng/ml, similar results were determined with the literature, at a rate

of 8-17% (36-38). Although alternative drugs have been developed, the toxicity of digoxin remains high, especially in 2019.

Phenobarbital SDC was toxic at a rate of 10%. This rate was found to be 11.5%, in a study conducted in Turkey (12). Phenobarbital has been used as a first-line treatment for epilepsy in neonates, despite limited efficacy and safety data (39). Phenobarbital is metabolized in the liver by cytochrome P450 (CYP) enzymes, and genetic polymorphisms in these enzymes may affect metabolism as well as elimination of phenobarbital (40). Therefore, both potential drug-drug interactions and interindividual differences are the factors affecting phenobarbital SDC (41). It requires attention in terms of high SDC, because it is an antiepileptic used especially in the newborn and pediatric age group. The fact that very high toxic concentrations of phenobarbital were found in the last two years in which the study data were collected indicates that attention should be paid to the safe use of this drug.

Patient demographics, such as age and sex, may affect SDC. In our study, SDCs were found to be higher for all drugs with increasing age. Similarly, Grzesk et al. determined significantly increased SDCs for digoxin by increasing age (42). In addition to the studies indicating higher rates of lithium SDC by increasing age, there are also studies reporting no significant difference (43). The finding of a significant increase in digoxin SDC with age and female sex was consistent with the literature (36). Women, compared to men, have a higher percent body fat weight, which may lead to differences in the distribution of drugs (44). Decreased muscle mass, water ratio and kidney functions in elderly individuals may cause changes in the distribution and especially excretion of drugs (45). The higher rates of SDCs detected by increasing age and female sex may be due to changes in the pharmacokinetics of the drug. However, the other patient-related factors that may affect the pharmacokinetics of the drug should also be considered.

The limitation of this study is the lack of patients' data including height, weight, other drugs used, comorbidities, serum albumin and electrolyte levels, kidney and liver function tests that may affect the pharmacokinetics of the drugs, and baseline demographic characteristics, prognostic factors such as mortality and hospitalization, or health care expenditures. Because they were not included in the electronic database between 2012 and 2019. Another limitation is that the study was carried out in a single center. The number of similar studies evaluating the SDC of all drugs is rather low and this study can be considered favourable due to the large number of data used in the analyses.

CONCLUSION

This study evaluated drug levels of both inpatients and outpatients admitted to a tertiary university hospital in a period of 8 years. SDC was determined high at subtherapeutic levels for phenytoin, lithium and digoxin; and at toxic levels for phenobarbital and digoxin. Although we cannot provide clinical outcomes, keep in mind that subtherapeutic levels may lead to treatment failure and poor prognosis, while toxic levels may lead to longer length of stay and higher mortality, development of additional comorbidities, and unnecessary health care expenditures.

It was observed that patient-related factors such as age and sex could affect SDC by changing the concentrations of the drug. This study evaluated only drug levels, TDM was not performed. Studies evaluating TDM specifically for the indications and the drugs will shed light on the subject.

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