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Saliva versus plasma therapeutic drug monitoring of carbamazepine in Jordanian patients

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ABSTRACT: Therapeutic drug monitoring (TDM) is a helpful method to make sure that drugs are prescribed, delivered, and experienced by patients at the intended therapeutic levels. There are several ways to carry out TDM. The TDM of carbamazepine utilizing salivary samples is not, however, supported by enough data. The aim of this study is to evaluate the possibility of utilizing salivary samples in place of plasma samples for the TDM of carbamazepine. In this study, an observational design was used. Where 14 patients in total took part. For comparison, carbamazepine plasma and salivary samples were taken at maximum and minimum levels. Carbamazepine levels were tested using calibrated LC MS-MS then ANOVA test was used for statistical analysis. Obtaining ethical permission came before sample collection. The minimum plasma and salivary levels concentrations were significantly correlated ($p = 0.025$, $r=0.59$). Maximum plasma and salivary levels of carbamazepine concentrations were significantly correlated ($p = 0.005$, $r=0.7$). AST was significantly correlated with maximum plasma carbamazepine concentrations ($p = 0.036$, $r = 0.8$). No other significant relationships were found between carbamazepine concentrations and sociodemographic characteristics. In conclusion, saliva samples can be used as an alternative to plasma samples while monitoring the therapeutic effects of carbamazepine. Compared to plasma TDM for carbamazepine, salivary TDM offers the benefit of being non-invasive and safer than blood sampling.

KEYWORDS: Salivary excretion classification system; therapeutic drug monitoring; carbamazepine; pk-sim.

1. INTRODUCTION

Carbamazepine ($C_{15}H_{12}N_2O$), an iminostilbene derivative related to tricyclic antidepressants, is used to treat tonic-clonic (grand mal) seizures as well as partial and secondary generalized seizures. It is used as a preventative measure in the long-term management of epilepsy. Trigeminal neuralgia and bipolar mood disorders can both be effectively treated with carbamazepine [1]. It is important to take carbamazepine exactly as prescribed by a healthcare professional and to alert them to any adverse effects or worries [2][3]. Carbamazepine has a narrow therapeutic window were the difference between an effective and hazardous dosage for carbamazepine is quite tiny, which makes TDM for this medication crucial [3][4].

1.1. Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) plays a vital role in optimizing patient treatment outcomes and minimizing side effects [4]. Due to their narrow therapeutic window, TDM is important in antiepileptic drugs and immunosuppressants [5]. TDM involves regularly collecting biological fluid samples, such as plasma, serum, saliva, or urine, to adjust drug dosages based on individual patient characteristics [2,6,7]. The individualization of drug therapy through TDM allows for tailored dosages based on factors such as age, BMI, and kidney and liver function [2,4,8,9]. Therapeutic drug monitoring is usually done using serum or plasma, matrices such as tears, sweat, urine or saliva could also be used in cases where the targeted drug is excreted in the other matrices in enough concentrations to be monitored.

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Samples for TDM are taken at predetermined intervals after drug administration, usually, the peak and trough levels of a drug's concentration are the two most frequently measured values. A drug's peak level is its maximum concentration after administration, whereas its trough level is the concentration at which it is at its minimum right before the next dosage is administered [10,11].

Once steady state is reached then blood and saliva samples are collected from patients prior to taking each dose of Carbamazepine and after; at tmax of 4-5 hours to compare plasma and saliva levels [1]. When choosing the method of analysis of carbamazepine both accessibility to equipment and the accuracy needed for the result and budget are taken into account; HPLC, GS, or immunoassays may be considered [12-14].

1.2. Salivary drug monitoring of carbamazepine

Saliva has advantages over serum for therapeutic drug monitoring (TDM), such as non-invasiveness and cost-effectiveness. Saliva can be a reliable sample for TDM of certain drugs, but variability and accuracy should be considered [15]. Salivary samples are stored at 4 °C for a maximum of 6 hours to prevent bacterial development and any degradation of the salivary contents. Samples also can be kept for years at -80 °C with almost no degradation [16] Recently studies have been concentrating more on detecting drugs in saliva, however, some drugs may not be suitable for monitoring through saliva due to low concentrations or poor correlation with plasma levels [17-19].

Research has been focusing on the detection of carbamazepine in saliva as a potential alternative for more conventional drug testing matrices including blood and urine [20]. Several studies done in the past has shown that carbamazepine can be detected in saliva. A study by W Schramm et al. done in 1991 showed that the ultrafiltrate of saliva can be used to simplify the diagnostic evaluation of circulating carbamazepine. Other studies such as a study by George W Rylance and Terence A Moreland done in 1981 on 35 children showed a significant relation between carbamazepine's dose and saliva levels. However, none of the previous studies measured carbamazepine's therapeutic range in salive nor detected relationship between carbamazepine and other sociodemographic characteristics.

In this study, the concentration of carbamazepine in saliva is measured and the normal salivary range is determined.

Drugs are categorized using the (SECS) based on their intestinal permeability and protein binding. The system categorizes medications into four classes; were class I drugs have high intestinal permeability and a high fraction unbound, class II drugs have low intestinal permeability and a high fraction unbound, class III drugs have high intestinal permeability and a low fraction unbound and class IV drugs have low intestinal permeability and a low fraction unbound [21]. The first three classes are excreted in saliva whereas class IV drugs are not excreted in saliva [21].

Carbamazepine's fraction unbound is 0.25 (fraction unbound is above 0.1) and effective intestinal permeability is in the range of (4.3x10-4 cm/sec) and according to the equation: Fa=1-e -2An (I), carbamazepine Fa equals 0.995 (Fa is higher than 0.9), based on the data carbamazepine is classified as SECS class I drug [21,22].

2. RESULTS AND DISCUSSION

2.1. Saliva versus plasma

The advantages of using saliva include the fact that it is a non-invasive procedure, painless collection, more cost-effective, and has ability to be collected remotely and does not require the expertise of a healthcare professional making it an attractive option for both patients and healthcare providers. Whereas plasma, in addition to it being painful, invasive and requires a healthcare professional to draw the sample can also be harder to collect in elderly patients or younger patients, or patients with other medical conditions.

2.2. Patient selection

14 patients in total 9 women (64.2%) and 5 men (35.7%) participated in the study. The sociodemographic information and clinical characteristics of the subjects are displayed in Table 1. Participants were 44 years old on average, ages ranging from 16 to 70 years old. The participant's weight ranges from 55 to 90 kilograms. All participants in the research were on long-term Carbamazepine therapy, were hospitalized at the time of data collection, and gave their informed consent. Age, weight, and creatinine levels were used for calculating creatinine clearance. Additionally, patient information including age, gender, and weight was obtained from medical records.

Table 1. Sociodemographic and clinical characteristics of participants (n = 14)

Patient Number	Age (Years)	Gender	Weight (kg)
1	45	F	55
2	16	F	57
3	47	M	90
4	42	M	62
5	43	F	70
6	67	F	69
7	30	M	80
8	31	M	77
9	56	F	65
10	59	F	70
11	56	F	65
12	70	F	65
13	17	F	88
14	36	M	70
Mean	44	-	70.5
SD	16.81		10.40
Range	16-70	-	55-90
Male %	35.7%	Female%	64.2%

2.3. Relationship between plasma and saliva carbamazepine concentrations

The minimum and maximum plasma concentrations of carbamazepine were measured for 14 patients who participated in the study. Minimum concentrations ranged from 2693.71 to 10037.82 ng/mL while maximum concentrations ranged from 3327.41 to 10131.30 ng/mL. Mean values for minimum concentrations were 5164.44 ng/mL (SD = 2099.27) and (CV% =0.406) while mean values for maximum concentrations were 6033.58 ng/mL (SD = 2215.97) and (CV% =0.367).

The minimum and maximum saliva concentrations of carbamazepine were measured for 14 patients who participated in the study. Minimum concentrations ranged from 106.88 to 3234.06 ng/mL while maximum concentrations ranged from 523.91 to 3027.74 ng/mL. Mean values for minimum concentrations were 1310.848 ng/mL (SD = 883.8552) and (CV% =2.29) while mean values for maximum concentrations were 1677.48 ng/mL (SD = 831.71213) and (CV% =0.588).

The values given were transformed into logarithmic values to correct the non-normal values from the sample collected then using the SYSTAT program. The correlations between plasma and saliva concentrations were measured and the p and R-values were calculated. First, a weak, non-significant, correlation was found between saliva and plasma AUC (area under the curve) for carbamazepine (r = 0.42, p = 0.133). p value was above 0.05 which is considered insignificant and r value shows an insignificant correlation the further from 1 the value is. Figure 1 shows the correlation between saliva and plasma AUC for carbamazepine.

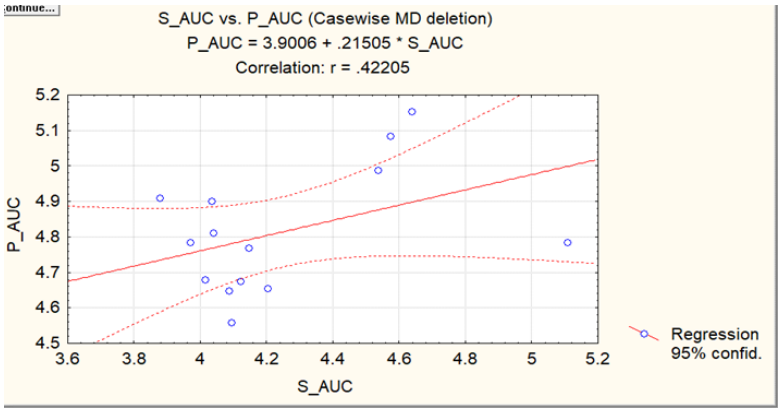

Figure 1. Correlation of saliva and plasma AUC of carbamazepine

The log-transformed minimum saliva and plasma concentrations of carbamazepine were found to be highly correlated (r = 0.59, p = 0.025). The relationship between the minimum plasma and salivary levels of carbamazepine is shown in Figure 2.

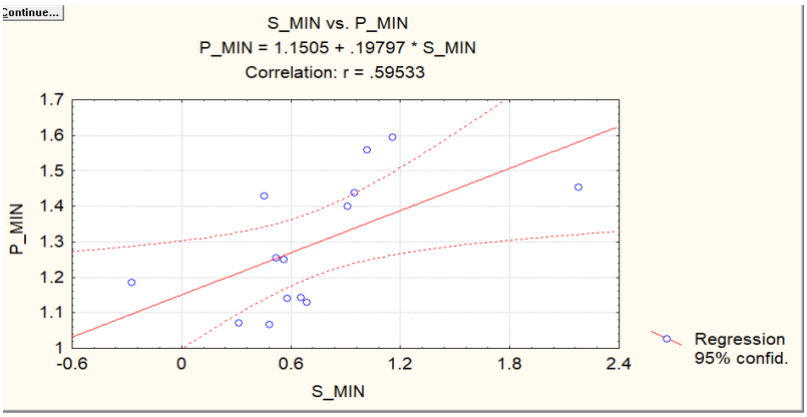

Figure 2. Correlation plots of minimum saliva and plasma concentrations of carbamazepine

Between the log-transformed maximal salivary and plasma levels of carbamazepine, there was a significantly strong correlation (r = 0.70, p = 0.005). Maximum plasma and salivary levels of carbamazepine are correlated in Figure 3.

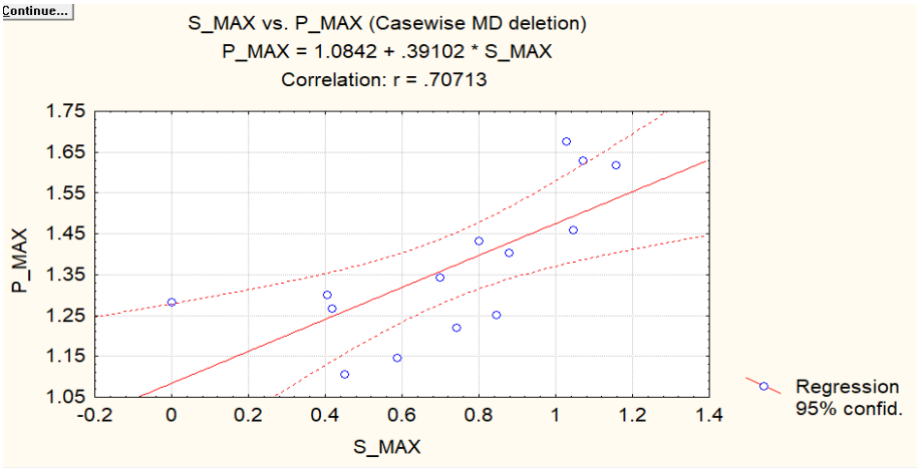

Figure 3. Correlation of maximum saliva and plasma concentrations of carbamazepine

Table 2 shows the details of saliva and plasma minimum and maximum concentrations and ratios.

Table 2. Ratios of minimum and maximum saliva concentrations of carbamazepine (n = 14)

	Plasma C_{min}	Saliva C_{min}	Plasma C_{max}	Saliva C_{max}	S_{min}/P_{min}	S_{max}/P_{max}
1	3567.43	726.37	4406.86	1000.86	**0.203612**	**0.227114**
2	7871.80	2881.83	8310.99	2868.01	**0.366095**	**0.345086**
3	2693.71	969.75	3327.41	1106.24	**0.360005**	**0.332463**
4	10037.82	3234.06	10131.30	3027.74	**0.322187**	**0.29885**
5	3625.82	1035.13	4261.41	1175.14	**0.285489**	**0.275763**
6	3073.02	106.88	3703.12	523.91	**0.03478**	**0.141478**
7	5526.29	1510.57	5601.55	1548.14	**0.273343**	**0.276377**
8	7190.86	1313.49	7977.38	1018.23	**0.182661**	**0.12764**
9	5683.56	29892.80	9502.61	2127.86	*	**0.223924**
10	2774.30	904.90	3835.27	0.00	**0.326172**	*
11	5499.56	1769.53	5762.29	2218.44	**0.321758**	**0.384993**
12	5367.45	565.09	5413.32	1260.96	**0.105281**	**0.232937**
13	4671.91	1204.01	5114.89	1127.22	**0.257713**	**0.22038**
14	4718.67	819.42	7121.72	2804.46	**0.173655**	**0.39379**

Normal plasma range	Normal saliva range	**$Average_{min}$**	**$Average_{max}$**
4000-12000 ng/ml	988-3213 **ng/ml**	**0.247135**	**0.267753**

*no data available

The theoretical ratio between saliva and plasma concentrations can also be calculated using the formula, the ratio was 0.299. When we calculated the normal saliva range by using the actual s/p ratio, the normal saliva range was 988-3213 ng/ml.

2.4. Effect of aspartate aminotransferase (AST) on carbamazepine plasma maximum concentrations

The maximal plasma carbamazepine concentrations after log transformation to normalise the data and the AST were investigated for correlation to see whether there were any significant correlations. Maximum plasma carbamazepine concentrations and AST were observed to be significant with a strong correlation (r = 0.80, p = 0.036) in Figure 4 . This can be due to the high liver metabolism of carbamazepine.

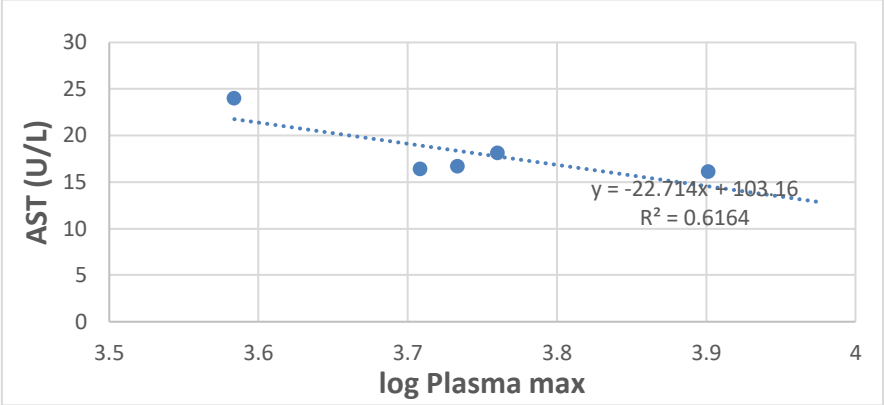

Figure 4. Correlation of log maximum plasma concentrations of carbamazepine with aspartate aminotransferase (AST).

2.5. Effect of other variables on carbamazepine maximum concentrations

Table 3 shows the significance of other variables on carbamazepine concentration and their p-value.

Table 3. Minimum and maximum saliva and plasma concentrations of carbamazepine and p- value for different variables (n = 14)

	Saliva (C_{min})	**Saliva (C_{max})**	**Plasma (C_{min})**	**Plasma (C_{max})**
AGE	0.169	0.744	0.7	0.686
ALB	0.152	0.448	0.965	0.973
ALT	0.072	0.111	0.12	0.133
AST	0.259	0.263	0.163	0.036
GENDR	0.219	0.804	0.701	0.704
HB	0.931	0.963	0.438	0.581
PLT	0.495	0.913	0.683	0.473
UREA	0.352	0.974	0.387	0.666
WBC	0.209	0.467	0.913	0.7
WT	0.219	0.124	0.598	0.449
Cr	0.238	0.461	0.496	0.332

3. CONCLUSION

The findings of this study indicated that saliva samples can be used as a substitute for plasma samples in the therapeutic drug monitoring of carbamazepine. As there was a significantly strong correlation (r = 0.70, p = 0.005) for maximum plasma and saliva concentrations of carbamazepine, minimum saliva and plasma

concentrations of carbamazepine were also found to be significantly strongly correlated (r = 0.59, p = 0.025). When studying other parameters and there effect on carbamazepine concentration, AST had a strong effect on maximum plasma carbamazepine concentrations. There was a significantly strong correlation between AST and maximum plasma carbamazepine concentrations. However other parameters including age, gender, weight, albumin, [ALT], kidney function test, [WBC], [PLT], and [HB] did not affect carbamazepine concentrations. Tests showed no significant relationships or differences in carbamazepine concentrations.

4. MATERIALS AND METHODS

4.1. Chemicals and reagents

The standards used in the analysis are carbamazepine and carbamazepine-d10 as the internal standard. Purified water and HPLC/SPECTRO grade methanol are the required reagents.

4.2. Chromatographic conditions

The chromatographic conditions for the method described in the study include the use of specific materials, standards, reagents, and apparatus. The apparatus used in the analysis includes micropipettes of different volumes (10-100 µL, 20-200 µL, and 100-1000 µL), a vortex mixer (IKA) for 36 samples, an Eppendorf centrifuge 5810 R, RAD WAG and Mettler Toledo analytical balances, a freezer at -20 ^{o}C, a refrigerator at 2-8 ^{o}C, a synchronized clock timer, a dual-timer clock, an Eppendorf dispenser (1-5), and a stable temperature water bath**.**

The HPLC components used in the analysis include an Agilent 1260 or Agilent 1260/1290 Series pump and auto-sampler, an API 5500 Applied Biosystems detector, an ACE C18 5□m, 4.6 x 50 mm analytical column, and the Analyst 1.6.3 data system.

The specific chromatographic conditions for the analysis are as follows: a flow rate of 0.400 mL/min, a column temperature of 25 ^{o}C, an auto-sampler temperature of 5 ^{o}C, an injection volume of 5 microliters, and a total run time of 3.00 min.

The detection and retention times of the standards used in the analysis are approximately 1.90 min for carbamazepine (with a parent ion at 237.200 and daughter ion at 194.200) and carbamazepine-d10 (with a parent ion at 247.200 and daughter ion at 204.200).

4.3. Preparation of stock, intermediate and calibrators solutions

To prepare the solutions for carbamazepine analysis, various stock solutions and working solutions were prepared. The Master Standard Solution for carbamazepine was prepared by dissolving 25.0 mg of carbamazepine in 2 ml of dimethyl sulfoxide and completing the volume with methanol, resulting in a concentration of 1.00 mg/ml. The Master Standard Solution for the internal standard (IS), carbamazepine-d10, was prepared by dissolving the pre-weighed content of the carbamazepine-d10 vial in methanol, resulting in a concentration of 1.00 mg/ml.

From the Master solution of carbamazepine, a working solution with a concentration of 1.0 mg carbamazepine/ml was prepared by taking 5000 µl and diluting it to 25 ml with a diluent of methanol: water (50:50, v/v) and mixing it by vortex. This resulted in a concentration of 200.0 µg carbamazepine.

For the preparation of calibration standards, the carbamazepine working solution with a concentration of 200.0 µg/ml was used. Dilutions were made using a diluent of water: methanol (50:50, v/v) to obtain different concentrations, 10 calibration standards were prepared, with final concentrations being (200,400,800,2000,8000,20000,35000,40000,70000,100000) ng/ml.

In addition, a working solution of carbamazepine-d10 was prepared by taking 100 µl from the Master solution (1.0 mg carbamazepine-d10/ml) and diluting it to 100 ml with a diluent of water: methanol (50:50, v/v) and mixing it by vortex. This resulted in a concentration of 1000 ng carbamazepine-d10/ml.

A mobile phase was prepared by mixing 750 ml of methanol with 250 ml of purified water and shaking well. This resulted in a ratio of 75% methanol to 25% water.

The calibration standards and quality control samples were prepared by spiking plasma samples with the appropriate working solutions. The spiked samples were stored under the same conditions as the analyzed samples.

4.4. Preparation of quality control samples

For the Preparation of Calibration Standards, ten different concentrations of carbamazepine were achieved by using a working standard solution. Various volumes of this solution were spiked into total plasma volumes, resulting in final concentrations ranging from 20.00 ng/mL to 10,000.00 ng/mL.

The QC samples were prepared using working standard solutions at different concentrations. These solutions were spiked into total plasma volumesand saliva volumes, resulting in final QC concentrations ranging from 60.00 ng/mL to 7,500.00 ng/mL.

These Calibration Standards and QC samples serve as reference points with known concentrations of carbamazepine in plasma and saliva. They are essential for validating the accuracy and reliability of the analytical measurements during the analysis process**.**

4.5. Extraction of carbamazepine from plasma and saliva

Extraction of carbamazepine for saliva and plasma is done by measuring volume of either blank plasma or saliva, or spiked plasmaor saliva and is then pipetted into pre-labeled tubes. Then, a Serial Solution is added to the blank plasma or saliva, followed by the introduction of the Internal Standard Carbamazepine-d10 Working Solution. The samples are vortexed for approximately 10 seconds to ensure proper mixing. Next, Methanol is dispensed into each tube, and the samples are vortexed for 2.0 minutes. This allows for efficient extraction of the target analytes. To separate the extracted components, the tubes are centrifuged at 4000 rpm for 5.0 minutes at a controlled temperature of 25 ^{o}C. After centrifugation, a measured volume of the extracted samples is transferred into auto-sampler vials with inserts. The vials are then securely capped and transferred to the auto-sampler rack for subsequent analysis. These extraction steps ensure the isolation and concentration of the analytes of interest, enabling accurate and reliable results during the analysis process.6.6 Limits of quantitation (LLOQ).

According to the USFDA bioanalytical method validation guidance, the analytical method was developed and validated to measure the lowest concentration that can be identified with appropriate precision and accuracy. The precision of these limits was less than 20%, with the LLOQ in plasma and Saliva being 20.0 ng/ml.

4.6. Bioanalytical method validation

The mean peak areas of six extracted Low, medium, and high-quality control samples were compared to the mean peak areas of six pure reference solutions to assess carbamazepine recovery in plasma and saliva (unextracted). The mean peak areas of extracted samples were compared to the mean peak areas of neat standard solutions (unextracted) of the same concentration to assess carbamazepine recovery. The recovery results were around 83% for carbamazepine in human plasma and 92% in saliva, and all the replicates were acceptable because the precision (CV %) at each level was less than 15%.

4.7. Selectivity and specificity

The selectivity and specificity of the method were evaluated to confirm the absence of interfering substances around the retention time of the analyte. No interferences were observed at the retention time of both carbamazepine and the internal standard. The peaks exhibited good shape and were completely resolved from the Saliva components. The matrix peak was found to be less than 5% of the peak area of the internal standard, meeting the acceptability criteria as per the US FDA guidance.

4.8. Data analysis

4.8.1. Physiologically-based PK-sim modelling of carbamazepine

PK-sim simulation is a software that simulates and help predict the pharmacokinitecs of the drug in different mammalian models based on their physiochemical properties. It has been used to simulate carbamazepine's single oral dose in a human model and give an initial indication regarding minimum and maximum concentrations to ease the therapeutic drug monitoring process. The physical and chemical properties of carbamazepine used are shown in Table 4 [22].

Table 4. Chemical and physical properties

Parameter	Literature	Unit
Molecular weight	236.27	g/mol
Lipophilicity	2.1	Log Units
Solubility	336	µg/mL
Fraction unbound%	25	%
Clearance hepatic	0.02	1/min
GFR fraction	0.03	
Intestinal permeability	4.3 × 10−4	cm/s
Partition coefficients	Rodgers and Rowlands	
Cellular permeabilities	PK-Sim Standard	cm/s

4.8.2. PK-sim simulation of carbamazepine

Figure 5 shows the PK-simulation of carbamazepine of plasma concentration vs time and observed data. For both the observed data and the pk-sim simulation, the concentration of carbamazepine is shown versus time in Figure 1. Overall, there was no difference between the findings of the simulation and the observed data, which were extremely similar.

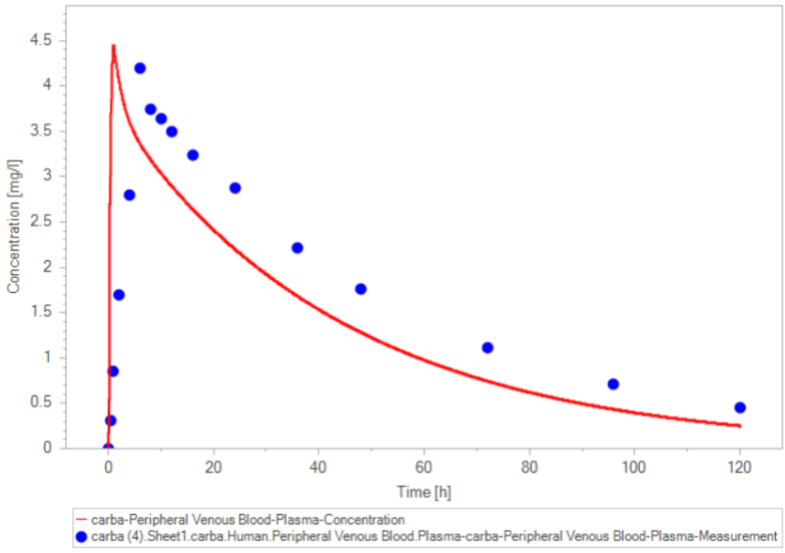

Figure 5. PK-simulation of carbamazepine of plasma concentration vs time and observed data [22]

4.8.3. Statistical analysis

The calculations were done using Excel for obtaining the mean, the standard deviation, the coefficient of variance, and ratio statistics. Systat version 5 was used for the ANOVA and Statistica version 4.5 was used for the correlation analysis and the calculation of the r and p values.

4.9. Participants' clinical data

Table 5 shows the clinical data for the participants of the study.

Table 5. Participants' clinical data

No	Dose mg	T (h)	Cr mg/dl	CrCl mL/min	ALT	AST	Urea	WBC(10^3 /mcL)	PLT (10^3/ uL)	HB (g/dL)	Albumin
1	200	12	0.45	136.46	23.8	35.2	2	8.6	274	9.5	*
2	200	12	0.64	129.54	27.5	22.7	4.4	6.92	304	11.9	*
3	200	12	0.59	194.47	17.8	23.4	2.6	8.88	268	17.5	43.2
4	400	12	0.65	128.75	34.6	34.5	3.8	6.62	200	13.3	38.5
5	100	12	8.10	9.89	*	*	13.7	12.6	87	10.6	*
6	200	24	1.25	47.35	12.1	18.5	9.5	7.93	204	12.2	*
7	400	8	0.70	174.45	*	*	4.1	9.3	317	10.7	*
8	400	8	0.54	214.91	11	16.1	5.2	15.7	422	12.4	47.1
9	200	8	0.44	146.26	*	*	5.8	5.03	201	13.1	*
10	200	24	0.71	93.74	17.2	24	6.9	8.16	324	14	37.43
11	200	8	0.44	146.26	16.9	18.1	5.8	5.52	220	13.1	*
12	200	12	0.46	115.94	13.9	16.7	14.5	16	287*10^9	8.3	2.26
13	400	12	0.61	209.41	10.2	16.4	2.2	6.6	164	13.8	*
14	400	24	12.59	8.02	*	*	29.6	5.8	44	8.4	29.5

*no data available

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Conflict of interest statement: The authors declared no conflict of interest.

REFERENCES

[1] Bauer LA (Ed.). Applied Clinical Pharmacokinetics, second ed. McGraw Hill, USA. 2008.
[2] Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma. Epilepsia. 2011; 52(4): 657-678. https://doi.org/10.1111/j.1528-1167.2011.03024.x
[3] Staffs of Lexi-Comp. Clinical Pharmacokinetics Pharmacy Handbook. Medical Books, USA. 2017.
[4] Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophrenia Bull. 2014; 40(2): 314-326. https://doi.org/10.1093/schbul/sbu001
[5] Piscitelli SC. The role of therapeutic drug monitoring in the management of HIV-infected patients. Curr Infect Dis Rep. 2002; 4: 353-358. https://doi.org/10.1007/s11908-002-0028-9

[6] Abdul-Aziz MH, Alffenaar JWC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, Neely MN, Paiva JA, Pea F, Sjovall F, Timsit JF, Udy AA, Wicha SG, Zeitlinger M, De Waele JJ, Roberts JA, Infection Section of European Society of Intensive Care Medicine (ESICM). Pharmacokinetic/pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Group of International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT), Infections in the ICU and Sepsis Working Group of International Society of Antimicrobial Chemotherapy. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper. Intens Care Med. 2002; 46(6): 1127-1153. https://doi.org/10.1007/s00134-020-06050-1

[7] Burtis CA, Ashwood ER, Bruns DE. Tietz textbook of clinical chemistry and molecular diagnostics. 5th ed. St. Louis, MO: Elsevier Saunders, USA. 2012.

[8] Landmark JC, Johannessen SI, Patsalos PN. Therapeutic drug monitoring of antiepileptic drugs: current status and future prospects. Expert Opin Drug Metabol Toxicol. 2020; 16(3):227-238. https://doi.org/10.1080/17425255.2020.1724956

[9] Kang JS, Lee MH. Overview of therapeutic drug monitoring. Korean J Int Med. 2009; 24(1): 1-10. https://doi.org/10.3904/kjim.2009.24.1.1

[10] Dasgupta A, Therapeutic drug monitoring. In A. Dasgupta (Ed.), Accurate Results in Clinical Laboratories: A Guide to Error Detection and Correction. Elsevier, USA. 2013, pp. 119-144.

[11] El-Bilbeisi H, Wilson AM. Therapeutic drug monitoring. In: Basic Pharmacokinetics and Pharmacodynamics: An Integrated Textbook and Computer Simulations. Wiley, USA. 2013.

[12] Clarke W, Immunoassays for therapeutic drug monitoring and clinical toxicology. In: Handbook of Analytical Separations, Vol. 7. Elsevier BV. 2020, pp. 97-114. https://doi.org/10.1016/B978-0-444-64066-6.00005-8

[13] Datar PA. Quantitative bioanalytical and analytical method development of dibenzazepine derivative, carbamazepine: A review. J Pharm Anal. 2015; 5(4): 213-222. https://doi.org/10.1016/j.jpha.2015.02.005

[14] Gaspar VP, Ibrahim S, Zahedi RP, Borchers CH. Utility, promise, and limitations of liquid chromatography-mass spectrometry-based therapeutic drug monitoring in precision medicine. J Mass Spect. 2021; 56(11): e4788. https://doi.org/10.1002/jms.4788

[15] Punj A. Secretions of Human Salivary Gland. Salivary Glands - New Approaches in Diagnostics and Treatment. IntechOpen, 2019. https://doi.org/10.5772/intechopen.75538

[16] Bhattarai KR, Kim HR, Chae HJ. Compliance with saliva collection protocol in healthy volunteers: Strategies for managing risk and errors. Int J Med Sci. 2018; 15(8): 823-831. https://doi.org/10.7150/ijms.25146

[17] Alvarado A, García G, Morales A, Paredes G, Mora M, Muñoz AM, Pariona R, Bendezú MR, Chávez H, García JA, Laos-Anchante D, Loja-Herrera B, Bolarte-Arteaga M, Pineda M. Phenytoin concentration in people with epilepsy: a comparative study in serum and saliva. Pharmacia. 2022; 69(3): 809-814. https://doi.org/10.3897/pharmacia.69.e87168

[18] Ghareeb M, Gohh RY, Akhlaghi F. Tacrolimus concentration in saliva of kidney transplant recipients: Factors influencing the relationship with whole blood concentrations. Clin Pharmacokinet. 2018; 57(9): 1199-1210. https://doi.org/10.1007/s40262-017-0626-1

[19] Navazesh M. Methods for collecting saliva. Ann New York Acad Sci. 1993; 694(1): 72-77. https://doi.org/10.1111/j.1749-6632.1993.tb18343.x

[20] Patsalos PN, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs by use of saliva. Therap Drug Monitor. 2013; 35(1): 4–29. https://doi.org/10.1097/ftd.0b013e31827c11e7

[21] Idkaidek N, Arafat T. Saliva versus plasma pharmacokinetics: Theory and application of a salivary excretion classification system. Mol Pharmaceutics. 2012; 9(8):2358–2363. https://doi.org/10.1021/mp300250r

[22] Kovačević I, Parojčić J, Homšek I, Tubić-Grozdanis M, Langguth P. Justification of biowaiver for carbamazepine, a low soluble high permeable compound, in solid dosage forms based on IVIVC and gastrointestinal simulation. Mol Pharmaceutics. 2009; 6(1): 40–47. https://doi.org/10.1021/mp800128y