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Original Article

Population Pharmacokinetic Study of Gabapentin in Iranian Healthy Volunteers

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Abstract

The objective of the study was to evaluate the pharmacokinetics of a single oral dose of 300 mg gabapentin capsule in an Iranian healthy population. The study was a standard two-way, crossover, randomized, and single-dose study with one-week washout period in 24 healthy volunteers who received 300 mg gabapentin capsules (test and reference formulation). After drug administration, blood samples were taken according to the planned times over a period of 24 hours. The plasma concentrations of gabapentin were determined using the validated high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection. All the pharmacokinetic parameters for gabapentin in healthy volunteers were calculated using nonlinear mixed-effect modeling and standard non-compartmental methods. A one-compartment model with a first-order absorption rate and first-order elimination rate with a proportional error model described the pharmacokinetics of gabapentin. Values (relative standard error (RSE) %) for first-order absorption rate constant (Ka), oral clearance (Cl/F), and apparent volume of distribution (V_d/F) were 1.08 (7.23) 1/h, 6.72(0.29) L/h, and 73.82(5.10) L. The mean estimate for non-compartmental pharmacokinetic parameters including maximum plasma concentration (C_{max}), the area under the curve to the last quantifiable concentration (AUC_t), and the area under the curve to the infinity (AUC_{inf}) was calculated. C_{max} for test and reference formulation was 3850 ng/mL and 3856 ng/mL respectively. The AUC_t for test and reference formulation was 39549 ng. h/mL and 40249 ng. h/mL respectively. The AUC_{inf} for test and reference formulation was 47161 ng. h/mL and 633424 ng. h/mL respectively. The median (range) for the time to peak plasma gabapentin concentration (T_{max}) for the test and reference drug was 3 (1.5-6) hours and 3 (1.5-5) hours respectively. The mean (standard deviation) elimination half_life ($t_{1/2}$) of gabapentin for the test and reference drug was 9.39 (2.75) hours and 8.88 (2.48) hours. They were all within the acceptable range of 80-125%, consequently, we concluded that the two gabapentin formulations were bioequivalent. Our results confirmed that the gabapentin pharmacokinetic model in the Iranian healthy population was similar to other studied populations. However, we could not find any influential covariate to explain the inter-individual variability of parameters.

Keywords: Gabapentin, Pharmacokinetics, Iranian population, Healthy subjects.

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1. Introduction

Gabapentin is a γ-aminobutyric acid (GABA) mimetic, works by reducing the activity of a subset of calcium channels [1]. It is an anticonvulsant drug used primarily to treat minor seizures and neuropathic pain [2-4].

Also, gabapentin has a well-recognized clinical efficacy in treating epilepsy, hot flashes, post-herpes neuralgia, and restless leg syndrome [5-8].

The gabapentin molecule ($C_9H_{17}NO_2$) has high aqueous solubility, low lipophilicity, and a lack of significant tissue binding, and plasma protein binding [1]. It showed saturable absorption and the rate of absorption is influenced by the absence or presence of the gastrointestinal tract transporter(s) [9, 10]. The bioavailability of gabapentin is dose-dependent and was shown to decrease with increasing doses [10]. The peak plasma concentration of gabapentin takes place about 3 hours after taking the oral dose, and the elimination half-life is approximately 5 to 9 hours [11]. Gabapentin is not metabolized and is excreted unchanged in the urine, also its clearance is highly correlated with renal function [11, 12].

Gabapentin population pharmacokinetics (PK) has been studied in infants, and children (healthy subjects, and patients with epilepsy)[13]. More ever, previous PK studies evaluated different doses of gabapentin in adult healthy subjects [14-18]. In addition, the population PK of gabapentin was studied in adults with chronic and neuropathic pain [19-21]. Nevertheless, the PK of this drug has not been studied in the Iranian population. This study aimed to evaluate the pharmacokinetics of gabapentin following single dosing in the Iranian healthy population using nonlinear mixed-effect modeling and standard non-compartmental methods.

2. Materials and Methods

2.1. Material

The standard of gabapentin (purity 100%) was from Medichem (Barcelona, Spain) and kindly provided by Sobhan Daru pharmaceutical company (Rasht, Iran). 1-Fluoro-2,4-dinitrobenzene (FDNB), and amlodipine as internal standard (I.S) were from Sigma Aldrich (St. Louis, MO, USA). Methanol, acetonitrile, dichloromethane, sodium hydroxide, sodium dihydrogen phosphate, triethylamine, phosphoric acid, and sodium sulfate all were HPLC grade and purchased from Merck (Darmstadt, Germany). Water was glass-double distilled and further purified for HPLC with a Maxima purification system (USF ELGA, England).

2.2. Study Design and Subjects

The study was conducted in a single-dose, two-period, open-label, and randomized crossover. Twenty-four healthy volunteers of both sexes were joined in the study. Body mass index (BMI), body surface area (BSA), lean body mass (LBM), and body fat were calculated for each volunteer. All volunteers had no history of diseases affecting the gabapentin pharmacokinetic processes and no other medication was normally given to the subjects for at least 1 week before the study. The major exclusion criteria for the study were smoking and pregnancy. After clearing up the purpose of the study, all individuals signed an informed consent form. The institutional ethics committee of Hamedan University of Medical

Sciences approved the study and the study is registered in the Iranian Registry of Clinical Trials (Protocol number: IRCT201511058022N3).

The subjects were in the fasting state (overnight fast of at least 10 hours) before drug administration and they continued to fast for up to 4 hours after dosing. They were given a normal breakfast, lunch, and an evening meal during the blood sampling. No other food was allowed during the time of the study. All subjects were given, orally, one capsule of two different formulations of gabapentin 300 mg capsules including Gabax (Sobhandarou, Rasht, Iran) as test formulation, or Neurontin (Pfizer, New York, USA) as reference formulation. Blood samples were drawn immediately before taking the drug (zero time), and 0.5, 1.5, 2, 2.5, 3, 4,5, 6. 8, 10.12, and 24 hours after dosing, to evaluate pharmacokinetic parameters.

2.3. Analytical Method and Sample Preparation

Gabapentin plasma concentration was assayed by a validated high-performance liquid chromatography (HPLC) method which was described earlier with some minor modifications [22]. The chromatographic system which was used consisted of two high-pressure pumps (LC-10AD), a column oven (CTO-10A), a UV detector operated at a wavelength of 360 nm, a degasser (DGU-3A), and a data processor (C-R4A) all from Shimadzu (Kyoto, Japan). The analytical column was a Shimpack CLC-C18 (Shimadzu, Kyoto, Japan), 250 mm × 4.6 mm I.D., 5 μm particle size, which was protected by a Shim-pack G-C18 guard column (10 mm × 4.0 mm I.D., 5 μm particle size).

The gabapentin derivation with FDNB was optimized using solutions of 5μg/ml of the gabapentin in the presence of amlodipine as I.S. In optimized condition, 30μl of reagent was used and the reaction mixture was kept at 65 ^{o} C for 10 minutes.

Different standard solutions of the gabapentin within the concentration range of 0.05–6 μg/mL were prepared in distilled water from a stock solution of gabapentin (1000 μg/mL). Amlodipine working standard (100 μg/mL), and an FDNB solution (0.012 M) were prepared in acetonitrile. Borate buffer (0.25 M) containing potassium chloride (0.25 M) was prepared in water and the pH was adjusted to 8.2. Hydrochloric acid solution (1 M) was prepared by diluting a hydrochloric acid (12 M) commercial solution.

Three series of calibration solutions were prepared by spiking 50μL of gabapentin standard solutions and 50μl of I.S. Plasma protein precipitation was done by adding acetonitrile and sample preparation steps were done as described earlier at optimized conditions [22].

2.4. Analytical Method Validation

The procedure was validated in terms of selectivity, linearity (calibration curve), accuracy, precision, recovery, matrix effect, and stability according to the guidelines of the Food and Drug Administration [23]. The lower limit of quantification (LLOQ) was considered as the concentration with a signal-to-noise ratio of 10.

2.5. Pharmacokinetic and Statistical Analysis

All plasma concentration-time points were used to set up the PK models. Both compartmental and non-compartmental PK parameters were calculated. The one- and two-compartment models were tried with and without the addition of the lag time (Tlag) parameter. The logarithmic distribution for all parameters was considered. The exponential model was used to describe each PK parameter's inter-individual variability (IIV). Additive, proportional, and combination (additive + proportional) error models were tested for residual variability. The data were analyzed using Monolix software, version 2020R1 (Lixoft, France), with the stochastic approximation expectation-maximization (SAEM) algorithm for nonlinear mixed-effects models.

COSSAC (Conditional Sampling used for Stepwise Approach based on Correlation tests) algorithm of Monolix software was used for covariate model building [24]. The tested covariates were formulation, age, sex, height, actual body weight, BMI, body fat, LBM, and BSA. The best covariate model was selected based on the smallest objective function value (OFV), Akike information criteria (AIC), Bayesian information criteria (BIC), and corrected Bayesian information criterion (BIC) [25].

The standard noncompartmental technique was used to estimate pharmacokinetic parameters such as maximum plasma concentration (C_{max}), the time to peak plasma concentration (T_{max}), the elimination rate constant (k_e), and the elimination half-life ($t_{1/2}$). Additionally, the linear trapezoidal rule was assumed to determine the area under the curve to the last quantifiable concentration (AUC_t) and infinity (AUC_{inf}). The data were statistically analyzed by analysis of variance (ANOVA) on the log-transformed AUCs and C_{max}. For establishing bioequivalence, both AUCs and C_{max} of the test product must be in 80%–125% of the reference product using a 90% Confidence interval (CI) of the test/reference mean ratios for PK parameters that were calculated. Microsoft Excel 2019 and SPSS Version 24 were employed for statistical analysis.

2.6. Model Evaluation and Validation

Both statistical and graphical criteria were used for model evaluation. The relative standard error (RSE), expressed as a percentage of the estimate, shows the precision of the estimate. Goodness-of-fit plots including observed concentrations versus predicted concentrations, and individual weighted residuals (IWRES) against time after the dose and concentration were used to approve the suitability of models. A visual predictive check (VPC) plot with 1,000 simulated datasets and a bootstrap resampling method with replacement generated 1,000 bootstrap datasets, were used to evaluate the stability and robustness of the final population PK model. Results from the VPC were assessed using a graphical comparison of the simulated data overlaid observed data and the model was fitted repeatedly to each of the 1,000 bootstrap datasets. The median and 90% confidence

intervals of parameters obtained from this step with RSMLX 2.0 (Inria, France) package of R software, version 3.6.2 (Vienna, Austria) were compared with the final parameter estimates.

3. Results and Discussion

Twenty-two males and two females, between 22 to 48 years old with a BMI range from 19.75 to 25.46 were included in this evaluation. The mean estimated for BSA, LBM, and body fat were 1.94 (m^2), 60.39 (kg/m^2), and 21.97 % respectively. The summary of the volunteers' characteristics is presented in **Table 1.**

Table 1: The summary of the volunteers' characteristics (n=24).

Characteristic (units)	Value *
Volunteers (male%)	24 (91.66)
Age (year)	31.5 (7.14)
Weight (kg)	78 (14.44)
Height (m)	1.73 (0.10)
Body mass index (kg/m^2)	25.77(3.53)
Body surface area (m2)	1.94(0.22)
Body fat (%)	21.97(5.04)
Lean body mass (kg)	60.39(8.98)

* Values are presented as mean (SD) for continuous and number (or percentage) for categorical characters

3.1. Analytical Method Validation

The HPLC method for gabapentin analysis in plasma samples passed all criteria for method validation and the results are shown in **Table 2**. The percentage error values of both within- and between days were all less than 8.27%. The specificity test results confirmed the absence of a specific peak in the area of the drug and I.S., and there was no interference in the analysis of the drug by the blank samples.

Stock solutions of gabapentin and amlodipine were stable for at least 30 days when stored at 4°C. Derivative solutions were found to be stable (>95%) for at least 12 hours when the samples were kept at 4°C. After 60 days, of maintenance of the serum at −80 °C and following three thaw–freeze cycles, the stability of the drug was found to be 99.5% from the initial value. The LLOQ was 100 ng/mL. The standard calibration curves were linear over the 50–6000 ng/mL concentration ranges using a line-fit plot in regression analysis (**Figure 1**). Plasma

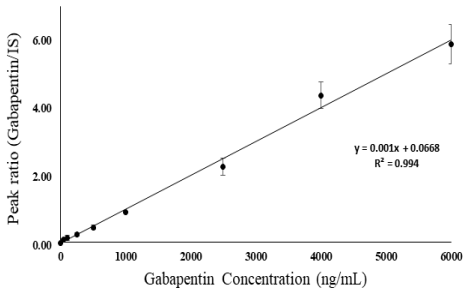

Figure 1: Linearity of the standard calibration curve of gabapentin in human plasma samples (n=3)

concentrations (Mean and standard deviation) of gabapentin at different time intervals after oral administration of a 300 mg capsule (Gabax and Neurontin) are shown in **Figure 2.**

Based on previous studies, several analytical methods are available to determine gabapentin concentrations in human plasma with HPLC [14, 22, 26, 27]. Despite trying the HPLC analysis method of gabapentin assay, described earlier by Bahrami et al [26], the mentioned method did not

Table 2: Recovery, within-day and between-day precision, and accuracy for gabapentin determination HPLC method in human plasma (n=3).

Plasma concentration (ng/mL)	Within-day		Between-day		Recovery	
	RSD*	Accuracy	RSD	Accuracy	%	RSD
100 (LLOQ)**	7.23	103.45	8.24	101.85	87.01	2.24
2500	3.14	99.25	8.27	96.39	73.22	2.11
6000	1.25	101.25	1.42	98.27	72.25	1.40

* Relative standard deviation, ** Lower limit of quantification

work. In this study, gabapentin determination with UV detection using FDNB as derivatizing reagent was chosen as the appropriate method with more sensitivity and reproducibility, ease of sample preparation, and availability in our laboratory in comparison to other approaches [22].

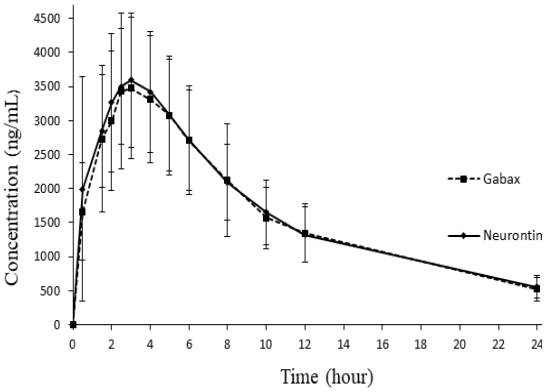

Figure 2: Plasma concentrations of gabapentin 300 mg capsules (Gabax and Neurontin) after oral administration to 24 healthy volunteers versus time. Each point represents mean ± SD.

3.2. Pharmacokinetic Analysis

Our study analyzed and reported the results of gabapentin 300 mg capsule pharmacokinetics in the Iranian health population. While previous pharmacokinetic studies evaluated different doses of gabapentin (300, 400, and 800 mg) in different populations including Korean, Indonesian, Thai, and Brazilian healthy subjects [14-18].

A total of 623 gabapentin concentration-time points were used to build the pharmacokinetic model. OVF, AIC, BIC, and BICc values for tested models are presented in **Table 3**. According to goodness-of-fit criteria, a one-compartment model with a first-order absorption rate and first-order elimination rate was selected as the final PK model and described our data in Iranian healthy populations, such as other populations (15-18, 20). However, a lag time that

Table 3: Goodness of fit criteria for tried gabapentin pharmacokinetic models in first-order absorption rate.

Tested Model	**OFV***	**AIC****	**BIC*****	**BICc ¶**
Two-compartments	8649	8673	8696	8710
Two-compartments + Lag time	8650	8674	8697	8711
One-compartment	8646	8660	8673	8681
One-compartment + Lag time	8661	8679	8696	8710

* Objective function value **Akike information criteria *** Bayesian information criteria ¶ Corrected Bayesian information criteria

frequently progresses the model fit by shifting the time of dosing was reported in the Korean population and the diabetic population [19, 28].

The PK parameters were first-order absorption rate constants (Ka), oral clearance (Cl/F), and oral volume of distribution (V_d/F). The population estimates for the final PK model parameters were 1.08 (1/h) for Ka, 83.72 (L) for V_d/F, and 6.72 (L/h) for Cl/F. The proportional error model described the residual variability in the final PK model. The inclusion of the covariates including formulation, age, sex, height, actual body weight, BMI, body fat, LBM, and BSA did not significantly improve the goodness of fit criteria. Estimated IIVs and residual variability are shown in **Table 4**.

Table 4: Final gabapentin pharmacokinetic model parameters and bootstrap results

Model	PK model	Bootstrap estimates	
Parameter (Units)	Mean estimate (RSE* %)	Median	Lower, Upper limit (90% CI**)
Ka*** (1/h)	1.08 (7.23)	1.08	1.047, 1.113
V_d/F ¶ (L)	73.82(5.10)	71.33	51.26, 91.40
Cl/F ¶¶ (L/h)	6.72(0.29)	6.18	4.14, 8.17
IIV ¶¶¶of Ka	0.29(20.40)	0.28	0.08, 0.48
IIV of V_d	0.24(15.60)	0.24	0.09, 0.39
IIV of Cl	0.2 (15.8)	0.21	0.06, 0.36
Residual variability			
b ^{S}	0.22(3.31)	0.22	0.19, 0.25

*Relative standard error, expressed as a percentage of the estimate. **Confidence interval ***First-order absorption rate constant ¶Oral volume of distribution. ¶¶ Typical value for clearance ¶¶¶ Inter-individual variability ^{S} Proportional error model parameter

The observed values of a gabapentin plasma concentration versus individual predicted values plots were almost equally scattered around the identity line (8.3% outlier), and are shown in **Figure 3**. The observations were randomly distributed within the calculated 90% prediction

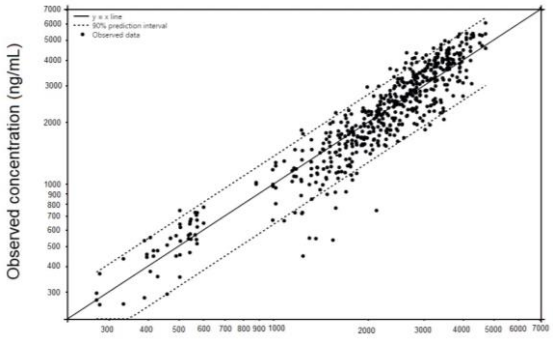

Figure 3: The goodness-of-fit plot of the final gabapentin PK model. Observed concentration versus predicted individual gabapentin plasma concentration (ng/mL).

intervals, showing no clear bias in the estimated population PK of the final model in the VPC plot shown in **Figure 4**. All the relationships between IWRES and time after the dose and concentration

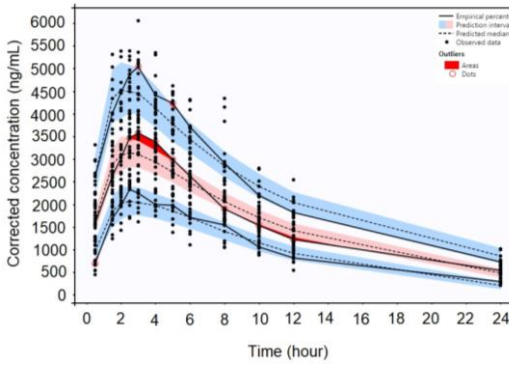

Figure 4: Visual predictive check (VPC) plot. Gabapentin plasma concentration (ng/mL) versus time after dosing (hour).

plots confirmed the adequacy of the final PK model (**Figure 5**). Also, the median values and the 90% confidence intervals of the parameter estimates obtained from 1000 bootstrap replicates of the original dataset included the population parameters of the final models and approved the

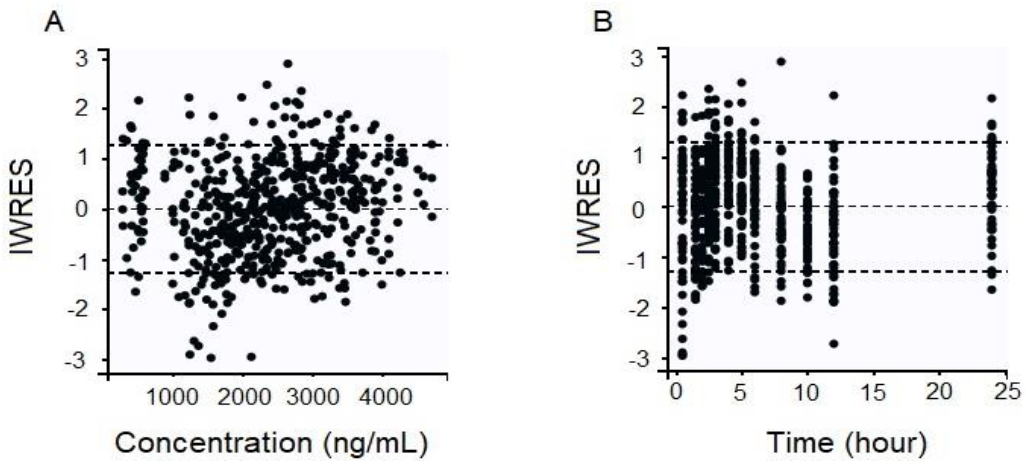

Figure 5: Individual weighted residuals (IWRES) versus A. gabapentin plasma concentration (ng/mL), and B. time after the gabapentin dosing (hour).

precision and robustness of the final PK model. The bootstrap validation results of PK estimates are shown in **Table 4**.

The mean estimate for the first-order absorption rate constant was 1.08 1/h which is statistically higher than the value reported in the healthy Korean population and patients with chronic pain [19, 28], and statistically equivalent to the absorption rate constant conveyed in hyperglycemic patients with neuropathic pain [20]. Inter-individual variability of Ka was 29%, which is considered approximately high Inter-subject variability, as declared by Gidal, Radulovic et al and Tran, Yoo et al [28, 29]. It has been reported that in healthy subjects, gabapentin showed saturable absorption likely because of saturation of the facilitated transport processes via LAT1 transporters [10]. It seems that ABCB1 2677G [T/A] polymorphism can explain the substantial inter-individual variability in the absorption of gabapentin [19, 28]. No significant effects of body size measures (BMI, BSA, body fat, and LBM), age, and sex were perceived on the absorption rate constant in the Iranian health population.

The calculated mean value for the oral volume of distribution was 83,72 L, with 24% inter-individual variability, which is statistically equivalent to other values reported in a different population [19, 28], however, the value reported in hyperglycaemic patients is meaningfully higher than V_d in Iranian healthy population (about 2 fold) [20]. Age and BMI are the factors that are supposed to influence the V_d parameter [30], while in the Iranian population, none of these variables had a significant effect on V_d/F.

The gabapentin Cl estimated in our population was 6.72 L/h with 20% IIV. This parameter was 2.93 L/h in elderly nursing home patients, 11.1 L/h in healthy Koreans, and 14.7 L/h in patients with chronic pain [19, 28, 31]. The results of a single-dose pharmacokinetics study of 400 mg gabapentin in healthy subjects, reported that changes in renal function are responsible for age-related changes in gabapentin pharmacokinetics and the pharmacokinetics of gabapentin were similar in men and women [32]. Furthermore, Gabapentin clinical pharmacokinetics is strongly influenced by creatinine clearance and it significantly influences

Table 5: Non-compartmental PK parameters of gabapentin formulation (test and reference) in healthy Iranian volunteers

Parameter	Gabax (Test formulation)		Neurontin (Reference formulation)	
	Mean (SD)	Median	Mean (SD)	Median
AUCt *	39549 (10920)	39071	40249 (8944)	38883
AUCinf**	47161(12747)	45321	633424(184405)	633501
Cmax***	3850(1083)	3869	3856(994)	3826
Tmax ¶	3 (1,5-6)	3	3(1.5-5)	3
t1/2¶¶	9.39(2.75)	8.35	8.88(2.48)	8.715

*Area under the curve to 24th hour (ng.h/mL) **Area under the curve to the infinity (ng.h/mL) ***Maximum plasma concentration (ng/mL) ¶ Time to reach peak plasma concentration (hour) ¶¶ Elimination half-life (hour)

the oral clearance of gabapentin [19, 20]. In our study, neither age nor gender did not show any significant effect on gabapentin Cl.

All non-compartmental PK parameters for the two formulations are listed in **Table 5**. In the present study, the AUC_t, AUC_{inf}, and C_{max} were the key parameters of gabapentin pharmacokinetics in the evaluation of expected bioequivalence between test and reference preparations. Based on our results all 90% CIs of the test/reference ratios for AUC_t, AUC_{inf}, and C_{max} of gabapentin lay in the acceptance ranges of bioequivalence (80-125%) **(Table 6)**. According to these results, two formulations were bioequivalent. The mean (standard deviation) elimination half-life of gabapentin for test and reference formulation were 9.39 (2.75) and 8.88 (2.48) hours, respectively, which were in line with other reported results in previous studies [4, 11, 16, 33]. It has been reported that T_{max} is a function of the gabapentin dose and the lowest dose of gabapentin (100 mg) was 1.7 hours, furthermore, it increases to 3–4 hours following a higher dose of gabapentin [9]. In Thai, healthy male volunteers received a single oral dose of 300 mg gabapentin capsule. AUCs and C_{max} were lower than our study, and T_{max} was statistically equivalent [18, 34].

Table 6: Summary of ANOVA analysis results of C_{max}, and AUCs for test and reference formulation of gabapentin

PK Parameter	**C_{max}**	**AUC_t**	**AUC_{inf}**
Ratio (test/reference)*	1.2	0.99	0.98
90% Confidence Interval	93.68-109.55	91.55-106.86	91.83-104.96

* Geometric means ratio

4. Conclusion

Our results confirmed that the gabapentin pharmacokinetic model in the Iranian health population was similar to the other studied population, and followed a one-compartment model with a first-order absorption rate and first-order elimination rate. However, we could not find any influential covariate to explain the inter-individual variability of parameters in this population. Furthermore, two gabapentin 300 mg capsules (test and reference) that were studied in volunteers were bioequivalent and could be used

interchangeably. Our study had limitations, such as a small number of subjects, a limited study population, and a limited range of covariates. Thus, more studies on patients are required to determine the pharmacokinetics of gabapentin. Our results might be useful to develop a population pharmacokinetic model in patients.

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Conflict of interest

The authors declare to have no conflict of interest.

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