Population pharmacokinetics of gabapentin in patients with neuropathic pain: the role of glycaemic control

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Abstract

Aims: Gabapentin (GBP) is an α2-δ ligand drug widely used to treat neuropathic pain, especially diabetic neuropathy. The drug presents a saturable absorption in therapeutic doses and it is mainly eliminated unchanged in the urine. GBP excretion has been suggested to be dependent on glomerular filtration rate and active transport by renal drug carriers. Our objective was to evaluate the role of diabetes and glycaemic control on GBP pharmacokinetics using a population pharmacokinetic modelling approach. Methods: A clinical trial was conducted in participants with neuropathic pain of intensity [?] 4 evaluated by visual analogue scale (VAS) (n=29), due to lumbar or cervical disc herniation or due to diabetic neuropathy. All participants were treated with a single oral dose of 300 mg GBP. Blood samples were collected up to 24 hours after GBP administration. A population pharmacokinetic analysis was conducted to evaluate the inter-individual variability considering as potential covariates weight, height, body mass index (BMI), sex, biomarkers of renal function and diabetes, and genotypes for the main genetic polymorphisms of SLC22A2 and SLC22A4, the genes encoding the transporters for organic cations OCT2 and OCTN1. Results: Population estimates for lag time, first-order absorption rate, total clearance and apparent volume of distribution at steady state were 0.32 h, 1.13 h-1, 14.7 L/h and 140 L, respectively. The total plasma clearance of GBP is affected by the estimated glomerular filtration rate and the volume of distribution increases with higher glycaemic levels. Conclusion: GBP population pharmacokinetics was affected by renal function and glycaemic control.

Introduction

Disease status has been recognized to affect drug pharmacokinetics and drug response [1-3]. In type 2 diabetes (DM2), chronic hyperglycaemia leads to protein glycation, alters gene expression and modulates epigenetics, which is associated with the "hyperglycaemic memory" [3-14]. Inflammation biomarkers in diabetes have been associated with complications of the disease, including nephropathy and neuropathy [15-19]. The complex effects of diabetes on pharmacokinetics are related to the altered physiology and changes in protein levels and/or activity of drug-metabolizing enzymes and transporters. Patients with poor glycaemic control in diabetes exhibit different pattern of pharmacokinetic alterations if compared with patients with diabetes and normal glycaemic levels, suggesting that glycaemic control plays an important role in pharmacokinetics [20-22].

Chronic hyperglycaemia affects the sympathetic and parasympathetic nervous systems, including functions linked to intestinal motility [23]. This may lead to reduced intestinal transit time in 20-50% of diabetic patients [23,24]. Depending on the status of diabetes-induced nephropathy, the glomerular filtration rate can be increased, unchanged or decreased [3]. Clinical and experimental studies have shown that diabetes changes the abundance or activity of drug-metabolizing enzymes and drug transporters [9,12,13,25-27]. Rats with DM2 induced by hypercaloric diet and streptozotocin [28,29] showed a 50% reduction in renal levels of organic cation transporter 2 (Oct2) [7]. The mRNA and protein levels of Oct1, Oct2 and Oct3 were lower in rats with diabetes [4,5]. High glycaemic levels were associated with increased P-glycoprotein expression in the gut and reduced expression in the kidneys [30,31]. Despite the potential effects of diabetes in pharmacokinetics, clinical data showing the role of glycaemic control on interindividual variability in drug plasma levels and pharmacokinetic parameters are scarce.

Gabapentin (GBP) is an organic cation drug commonly used as an add-on treatment for epilepsy and to treat diabetic neuropathic pain [32-36]. Randomized, double-blind, placebo-controlled clinical trials showed the efficacy of GBP to improve neuropathic manifestations [32,33]. GBP has a saturable absorption at the gastrointestinal tract and a variable bioavailability [25,26]. The drug is not metabolized in humans and it does not bind to plasma proteins [36-38]. The maximum plasma concentration of 2.7 μg/mL is reached between 2 and 3 hours, after a single dose of 300 mg GBP [39,40]. Its elimination is mainly renal as unchanged drug and partially dependent on renal tubular secretion mediated by the transporters for organic cations, mainly organic cation transporter novel 1 (OCTN1) and multidrug and toxin extrusion protein (MATE), but also the organic cation transporter 2 (OCT2) [41-44].

Considering the potential disease-drug pharmacokinetic interaction when diabetic neuropathic pain is treated with GBP, a prospective clinical trial was conducted to evaluate the effect of hyperglycaemia on GBP population pharmacokinetics. Patients diagnosed with neuropathic pain with score [?] 4 on a visual analogue scale (VAS), induced or not by diabetes, were investigated. The population pharmacokinetic analysis was conducted to evaluate the inter-individual variability and to test as covariates demographical and clinical variables, including biomarkers of renal function and diabetes, such as estimated glomerular filtration rate (eGFR) and glycaemic levels.

Methods

Participants

This clinical protocol and patient consent forms were designed following the revised Declaration of Helsinki and the Good Clinical Practice of the International Conference on Harmonization (ICH-GCP) and approved by the Ethics Committee of the School of Pharmaceutical Sciences of Ribeirão Preto and the School of Medicine of Ribeirão Preto, University of São Paulo (USP) (CAAE: 34175314.3.0000.5403). Thirty-two patients were invited to participate and provided written informed consent. The study was registered in Clinicaltrials.gov under the identifier NCT03047278.

Eligible subjects were adult patients (n=32), from 18 to 59 years old, with neuropathic pain with pain scores [?] 4 on VAS. All patients were recruited from the Pain Ambulatory or Diabetes Ambulatory of the Clinical Hospital of the School of Medicine of Ribeirao Preto, University of Sao Paulo (FMRP-USP) or from the Health Basic Unity (UBS) Cuiaba of the FMRP-USP. The diagnosis of neuropathic pain was based on the presence of daily moderate to severe chronic pain in the extremities for more than 90 days and a score of 4 cm (or greater than 4 cm) on a 10 cm visual analogue pain scale (0 = no pain; 10 = worst possible pain) [45,46]. The diagnosis of diabetes was based on the criteria by the American Diabetes Association [18]. Only participants with DM2 diagnosis for more than 6 months were included. Exclusion criteria were creatinine clearance [?] 30 mL/min, gastrointestinal diseases, history of alcohol or drug abuse and chronic use of medicines that interact with GBP. Three patients were excluded from the final analysis due to incomplete data.

Clinical Protocol

After 12 hours of fasting, all participants received a single dose of 300 mg GBP (Gabapentin, EMS, Hortolandia, Brazil) with 200 mL of water. Three hours after drug administration, non-diabetic participants received a standard meal and participants with diabetic neuropathic pain received a standard meal for diabetic patients. Serial blood samples were collected up to 24 hours after GBP administration and stored at -80 oC until the analysis. Blood samples (10 mL) were also collected to evaluate the clinical biomarkers: urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin (TB), fasting glucose levels (FGL) and glycated haemoglobin (HbA1c). The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine values using the CKD-EPI equation [47]. Whole blood was used for genotyping. All participants were genotyped for the SNPs 808G>T (rs316019) of *SLC22A2* gene and 1507C>T (rs1050152) of*SLC22A4* , as previously reported [44,48]. The Hardy-Weinberg (HW) equilibrium was evaluated using the Chi-square test (χ^2). The clinical history and the use of concomitant drugs were registered for all participants.

Analysis of GBP on plasma by HPLC-UV

GBP was determined in plasma by HPLC-UV (Shimadzu Inc., Kyoto, Japan), as described previously [44,48]. In summary, the analytes were resolved on LiChrospher® C18 RP column (125 × 4.0 mm, 5 µm, Merck, Darmstadt, Germany). The mobile phase consisted of 0.05 M sodium monobasic phosphate solution (pH 3.9):methanol (27:73, v/v), in a flow rate of 1.2 mL/min. The detection by ultraviolet was performed at λ= 360 nm. Plasma samples were prepared by protein precipitation with acetonitrile (ACN), followed by derivatization with 1-fluoro-2,4-dinitrobenzene (FDNB). Precision and accuracy, evaluated as relative standard deviation and relative errors, were below 15%, as well as the stability (evaluated in different conditions: short-term, long-term, post-processing and freeze-thaw cycles).

Population pharmacokinetic modelling

GBP concentration-time data were analysed using the nonlinear mixed-effects modelling software MONOLIX (Version 2019, Lixoft, France). Model development was based in 4 steps: selection of structural model; selection of an error model; covariate analysis and final model internal validation. The model selection was guided by the objective function value (OFV), represented as -2 times the log-likelihood (-2LL), relative standard errors (RSE) below 40% and unbiased goodness-of-fit plots [49-51]. One and two-compartment models, the inclusion of lag time and linear or Michaelis-Menten elimination were tested. A log-normally distributed interindividual variability (IIV) was tested on model parameters, whereas proportional, additive and combined error models were tested.

The following continuous covariates were evaluated: body weight, height, BMI, eGFR, HbA1c and FGL. Categorical covariates included sex, OCT2 and OCTN1 genotypes and the diabetes mellitus diagnostics. Potential covariates were evaluated by Pearson's correlation test or ANOVA. Covariates were included in the model using forward inclusion and backward elimination with a level of significance of $p < 0.05$ (ΔOFV > -3.84 points) and $p < 0.01$ (ΔOFV < 6.63), respectively. Additionally, the covariate inclusion had to reduce the unexplained IIV and improve the goodness-of-fit plots [49-51].

The model was internally validated using visual predictive check (VPC, n = 10.000 simulations) and bootstrap (n = 5.000 replicates) analysis, using the package Rsmlx for RStudio software (version 1.1.442, Free Software Foundation, Boston, USA).

Results

Participants

Twenty-nine patients with chronic neuropathic pain were enrolled and completed the study. The participants investigated here presented mean (standard deviation) age of 51.4 (6.5) years, body weight of 86.8 (19.9) kg, with a mean height of 164.9 (9.2) cm and a mean BMI of 31.8. (6.2) kg/m^2. All patients had eGFR > 30 mL/min/1.73m^2. In terms of the cause of neuropathic pain, 19 participants had diabetic neuropathy and 10 participants had neuropathic pain related to causes other than diabetes. Within the non-diabetic participants (n=10), 2 participants were diagnosed with cervical disc herniation and 8 with lumbar disc

herniation. Patients with diabetes presented either well-controlled diabetes with HbA1c < 8% (n=9) or poorly controlled diabetes with HbA1c [?] 8% (n=10). The reported mean basal pain on VAS was 7.9 (1.5) (Table 1). Individual demographic and biochemical characteristics were shown in Tables S1 and S2 (Supporting Information).

For the polymorphism 808G>T (*SLC22A2* gene), 22 participants were genotyped as wild-type homozygous (GG) and 7 were genotyped as heterozygous (GT), with a minor allele frequency (MAF) of 12%, which is consistent with the MAF of 11.9% found for the Brazilian population [52]. Eleven participants were genotyped as wild-type homozygous (CC) for the polymorphism 1507C>T (*SLC22A4* gene), 13 participants were genotyped as heterozygous (CT) and 5 were genotyped as mutant homozygous (TT), with a MAF of 39%, similar to the MAF of 32.9% found in the Brazilian population [52]. The genotype distributions of both polymorphisms were in Hardy-Weinberg equilibrium (Table S3 – Supporting Information).

Population pharmacokinetic modelling

The structural model was developed using 374 data of GBP plasma concentration. It consisted of a one-compartment with the inclusion of IIV on absorption constant (Ka), lag time, volume of distribution (Vd) and clearance (CL). The PK profiles are shown in Figure 1A. A correlation between the IIV of Vd and CL also improved the model. A proportional error model was best to estimate the unexplained residual variability rather than combined or additive error models. The estimates of lag time, Ka, Vd and CL were 0.32 h, 1.13 h^{-1}, 140 L and 14.7 L/h, respectively. The estimates of IIV expressed as RSE were 16.4% (lag time), 17.4% (Ka), 14.1% (Vd) and 13.4% (CL), respectively (Table 2).

Covariates selection was based on variables showing parameter-covariates relationship with p-value <0.05 (models No. 2-6, Table 3). Forward inclusion ended with four covariates; the OCTN1 genotype was not included because it resulted in high RSE (Table 3). Backward elimination was performed on the full model obtained and included the following covariates: a) eGFR on CL; b) body height and FGL on Vd. The addition of body height on Vd improved the model. Interestingly, other covariates with a strong correlation with height, such as BMI and weight, or covariates with better clinical explanation, such as weight, did not improve the model. Even though sex was included as a covariate on Ka on the forward inclusion step, it was removed on the backward elimination step.

The pharmacokinetic parameters of the final model and the bootstrap are presented in Table 2. The final model showed good predictive performance since RSE values were below 40%. The precision of the parameter estimates evaluated through bootstrap analysis showed that the zero value was not included in the 95% confidence intervals in any case. The absence of bias in the goodness-of-fit plots presented in Figure 1B-C illustrates the acceptable predictive value of the model.

Discussion

This was the first manuscript investigating the role of diabetes on GBP pharmacokinetics in humans. A population pharmacokinetic model was developed to investigate the influence of type 2 diabetes and glycaemic control and other potential covariates on GBP kinetic disposition. The pharmacokinetic estimates presented here are similar to parameter values previously reported for GBP, except for the lower values of volume of distribution and ka when compared to clinical trials with non-diabetic participants [44,48]. Our data showed that the volume of distribution of GBP was affected by body height and serum levels of glucose, while the total clearance was affected by eGFR (Table 3). GBP is primarily eliminated unchanged in urine and associations between eGFR and GBP pharmacokinetics have been reported previously [53-56].

Increased renal clearance of GBP was observed in rats with experimental diabetes induced by streptozotocin [57], suggesting that the effects of diabetes on the kinetic disposition of GBP occurred by inducing glomerular hyperfiltration [58]. While the experimental model of diabetes follows a strict protocol in rats in terms of duration of the disease, this clinical study includes patients with different levels of renal function and duration of diabetes. The results presented here have shown that eGFR is a covariate on renal clearance of GBP. This finding means that GBP kinetic disposition depends on the nephropathy level, which is indirectly related

to the glycaemic levels [59]. Among type 2 diabetic patients, 20 to 40% develop diabetic nephropathy (DN) [60], which consists of 5 steps: 1. Increase in eGFR and glomerular hypertrophy; 2. Hyperfiltration and microalbuminuria (> 30 mg/24 h); 3. Higher microalbuminuria (> 300 mg/24 h) and hypertension; 4. Microalbuminuria (> 300 mg/24 h), decrease on eGFR and increase in creatinine and blood urea nitrogen; 5. eGFR < 10 mL/min, which leads to haemodialysis [61]. A well-accepted theory for DN is that hyperglycaemia increases reactive oxygen species and pro-inflammatory cytokines [62-64].

Diabetes typically alters the expression and function of transporters for organic cations in mice with experimentally induced type 2 diabetes, probably due to the accumulation of end products of advanced glycation and inflammation [7]. Drug transporters for organic cations such as OCT2, MATE 1 and 2-K, and OCNT1 have been described to contribute to GBP renal excretion [43,44]. Although GBP has been described as an OCT2 substrate [42,43], the interaction with OCT2 is not relevant at therapeutic drug concentrations [44]. No significant changes in GBP kinetic disposition were observed after the coadministration of cimetidine (a known inhibitor of OCT2) or metformin (a known substrate of OCT2) in rats [57]. Moreover, cetirizine, an inhibitor of OCT2, MATE1 and 2-K [65,66], reduced the systemic exposure to GBP with no changes in renal clearance in patients with neuropathic pain, suggesting an interaction in the oral absorption process mediated by active transport (probably OCTN1) and not by renal drug transporters [44].

The effect of glycaemic control on the clinical pharmacokinetics of GBP observed here could be explained by the saturation of absorption processes, since the apparent volume of distribution is dependent on oral bioavailability [67,68]. OCTN1 is expressed in gut cells and might be responsible for the saturable absorption of GBP [69,70]. In type 1 diabetic mice, the renal protein expression of Octn1 is decreased [71]. The protein level of intestinal Octn1 follows a circadian rhythm, both in mice with diabetes induced by streptozotocin and in mice without diabetes [72]. However, there is no information in the literature about the impact of high glycaemic levels on the gut levels of OCTN1.

GBP intestinal uptake is mediated by L-type transporter (LAT) 2 [73-76] and by the system $b^{0,+}$ together with peptide transporter (PEPT) 1. These transporters might be associated with the saturable absorption of GBP [77]. Rats with experimental diabetes showed a reduction in the expression and activity of the pept1 transporter mRNA [78]. In rabbits with maternal diabetes induced by alloxan, the transcripts of LAT2 were increased in blastocysts, when compared to blastocysts of non-diabetic rabbits [79]. The reduction in the activity of PEPT1 by hyperglycaemia [76] seems to be a reasonable explanation for our findings which showed glycaemic level was a covariate in GBP apparent volume of distribution.

In therapeutic concentrations, the distribution of GBP to the central nervous system is regulated by LAT1 uptake [80]. The high concentration of glucose reduced LAT1 expression by 80%, compared to cells without the excess of glucose [81]. In opposition to the expected reduction on LAT1 expression, the effect of hyperglycaemia on LAT1 does not seem to influence GBP plasma concentrations since higher glycaemic levels are associated with lowering GBP plasma concentrations. Despite the lack of effect of LAT1 in GBP plasma levels, patients with uncontrolled diabetes could have an impact on drug concentrations in the effect compartment [75,82].

This work has some limitations. Firstly, participants were not genotyped for genetic polymorphisms of drug transporters involved in the absorption process of GBP. The polymorphisms c.438C>G (rs1060253) of the gene *SLC7A5* (LAT1) and 1347T>C (rs1339067) of the gene *SLC15A1* (PEPT1) are involved in risperidone and sirolimus pharmacokinetics [83,84]. Secondly, although the basal pain score on VAS was considered for inclusion of the participants, this study focused only on GBP pharmacokinetics. A population model relating pharmacokinetics to pharmacodynamics would be of great importance. Thirdly, the diabetes-induced epigenetic modifications on targets related to drug pharmacokinetics were not investigated. The possibility of a maintained lesion secondary to the hyperglycaemic memory [10,11] could not be ruled out to explain the changes in GBP clearance and volume of distribution in hyperglycaemic patients.

In conclusion, GBP population pharmacokinetics was influenced by renal function and by the serum levels of glucose. Genetic polymorphisms of OCT2 and OCTN1 transporters, sex, age, weight or BMI did not

influence GBP population pharmacokinetics. Our data suggest normal glycaemic levels in diabetic patients, achieved either by adherence to diabetes pharmacotherapy and changes in lifestyle (diet and physical exercise), reduces the variability in the kinetic disposition of GBP. In addition to the benefits related to diabetes comorbidities and patients' quality of life, the control of glycaemic levels is also relevant to achieve positive pharmacotherapy outcomes.

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Conflict of Interest

The authors of this paper declare that there are no conflicts of interests.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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Table 1. Demographic, clinical and genetic characteristics of participants with neuropathic pain investigated (n=29).

Characteristics	**Total (n=29)**
Age (years)	51.4 ± 6.5 53 (47.5, 57)
Sex	Men: 10 (34%) Women: 19 (66%)
Weight (kg)	86.8 ± 19.9 88.7 (75.1, 98)
Height (cm)	164.9 ± 9.2 164 (158, 173)
BMI (kg/m^2)	31.8 ± 6.2 32.5 (27.4, 37.1)
Neuropathic pain diagnosis	Cervical disc herniation (n=2) Lumbar disc herniation (n=8) Diabetic neuropathic pain (n=19)
Diabetes control	Well-controlled diabetes (HbA1c < 8%, n=9) Poorly controlled diabetes (HbA1c >8%, n=10)
Basal pain on VAS	7.9 ± 1.5 8 (7, 9.5)
Urea (mg/dL)	38.3 ± 20.6 32.4 (25.8, 41.2)
Creatinine (mg/dL)	0.92 ± 0.36 0.81 (0.67, 1.04)
eGFR ($mL/min/1.73m^2$)	85.5 ± 22.9 89 (72, 104)
AST (U/L)	21.9 ± 9.1 20.6 (16.1, 23.7)
ALT (U/L)	21.4 ± 8.9 19.5 (14.8, 27.1)
GGT (U/L)	40.6 ± 32.9 28.9 (21, 49.4)
TB (mg/dL)	0.52 ± 0.23 0.5 (0.4, 0.58)
FGL (mg/dL)	126 ± 54.4 110.8 (85, 156.3)
HbA1c (%)	7.3 ± 1.9 7 (5.6, 9.1)
Genotype for *SLC22A2* 808G>T (rs316019)	GG: 22 (76%) GT: 7 (24%)
Genotype for *SLC22A4* 1507C>T (rs1050152)	CC: 11 (38%) CT: 13 (45%) TT: 5 (17%)

Data presented as mean ± standard deviation, median (25, 75 percentiles). BMI: body mass index; HbA1c: glycated haemoglobin; VAS: visual analogue scale; eGFR: estimated glomerular filtration rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; TB: total bilirubin; FGL: fasting glucose levels; HbA1c: glycated haemoglobin; GG/CC: wild homozygous; GT/CT: heterozygous; TT: mutant homozygous.

Table 2. Parameter estimates and bootstrap results of the final model of GBP in patients with neuropathic pain due to lumbar/cervical disc herniation (n=10) or due to type 2 diabetes mellitus (n=19).

Parameter	**Estimate (RSE %)**	**Bootstrap analysis Estimate (95% CI)**
Structural model parameters		
Lag time (h)	0.32 (10.4)	0.32 (0.24-0.38)
Ka (h^{-1})	1.13 (10.3)	1.13 (0.89-1.47)
Vd (L)	140 (6.19)	140 (123-158)
CL (L/h)	14.7 (7.02)	14.7 (12.8-17.0)
Covariates		
Height on Vd*	2.17 (33.0)	2.17 (0.39-3.82)

Parameter	Estimate (RSE %)	Bootstrap analysis Estimate (95% CI)
FGL on Vd*	0.32 (36.4)	0.31 (0.08-0.63)
eGFR on CL**	0.53 (29.2)	0.53 (0.08-0.88)
Interindividual variability (IIV)		
Lag time	0.49 (16.4)	0.49 (0.21-0.78)
Ka	0.47 (17.4)	0.47 (0.23-0.67)
Vd	0.32 (14.1)	0.32 (0.20-0.40)
CL	0.37 (13.4)	0.37 (0.28-0.44)
Correlation between CL and Vd	0.82 (8.24)	0.82 (0.56-1.00)
Residual variability		
Proportional (%)	0.18 (4.89)	0.18 (0.15-0.22)

RSE: relative standard error; CI: confidence intervals; Ka: first-order absorption rate constant; Vd: volume of distribution; CL: clearance; eGFR: estimated glomerular filtration rate; FGL: fasting glucose levels. *: $Vd = PopVd \times \log(height/164)^{2.17} \times \log(FGL/110.8)^{0.32}$; **: $CL = PopCL \times \log(eGFR/89.0)^{0.53}$.

Table 3. Forward inclusion of covariates model building.

No.	Model	-2LL	Δ-2ΛΛ	Compared with
1	No covariate (basic model)	2641.94	-	-
2	eGFR on CL	2629.60	-12.34	1
3	FGL on Vd	2637.68	-4.26	1
4	Height on Vd	2632.28	-9.66	1
5	Sex on Ka	2636.56	-5.38	1
6	OCTN1 on Ka	2633.45	-8.49	1
3	eGFR on CL, FGL on Vd	2623.84	-5.76	2
4	eGFR on CL, FGL and height on Vd	2616.70	-7.13	3
5	eGFR on CL, FGL and height on Vd, sex on Ka	2610.35	-6.35	4

eGFR: estimated glomerular filtration rate; FGL: fasting glucose levels; OCTN1: organic cation transporter novel 1; CL: clearance; Vd: volume of distribution; Ka: first-order absorption rate constant; -2LL: 2 × log-likelihood.

Figure legends

Figure 1. Diagnostic plots for gabapentin pharmacokinetic final model. (A) Observed *vs.* population and individual predicted GBP concentrations. Linear regression fit is shown in black, whereas identity line in grey. (B) Population and individual weighted residuals (PWRES and IWRES, respectively) *vs.* time (upper panels; left) and*vs.* predictive GBP concentrations (lower panels; left); Normalized and prediction distribution error (NPDE) *vs.* time and GBP concentrations for the final model (right). The observed data are presented as black circles. (C) Visual predictive check (VPC) plot for the final model. The observed data are presented as black circles. The dashed lines represent the 5^{th}, $50^{th}$and 95^{th} percentiles of the predicted data. The grey areas represent the 95% confidence interval of predicted percentiles.