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The role of organic cation transporter 2 inhibitor cimetidine, experimental *diabetes mellitus* and metformin on gabapentin pharmacokinetics in rats

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ABSTRACT

Purpose: We investigated the influence of diabetes mellitus (DM), glycemic control with insulin, cimetidine (Oct2 inhibitor) and metformin (Oct2 substrate) on the kinetic disposition of GAB in rats.

Main methods: Male Wistar rats were divided in five groups and all animals received an oral dose of 50 mg/kg GAB: (vehicle + GAB), cimetidine + GAB (single dose of cimetidine [100 mg/kg] intraperitoneally 1 h before GAB), metformin + GAB (single dose of metformin 100 mg/kg by gavage concomitantly with GAB), DM + GAB (single dose of 40 mg/kg streptozotocin (STZ) intravenously) and DM + GAB + insulin (single dose 40 mg/kg STZ intravenously and 2 IU insulin twice daily for 15 days). Pharmacokinetic analysis was based on plasma and urine data concentrations.

Key findings: No differences in pharmacokinetic parameters were observed between vehicle + GAB × cimetidine + GAB and vehicle + GAB × metformin + GAB groups. Diabetes increased the fraction of GAB excreted unchanged in urine (vehicle + GAB: 0.48 [0.38–0.58]; DM + GAB: 0.83 [0.62–1.04]; DM + GAB + insulin: 0.88 [0.77–0.93]) (mean [95% confidence interval]) without any changes in GAB exposure. Insulin treated diabetic animals showed higher renal clearance compared to control (vehicle + GAB: 0.25 [0.18–0.30] L/h·kg; DM + GAB + insulin: 0.55 [0.45–1.43] L/h·kg), which was attributed to the diabetes-induced glomerular hyperfiltration.

Significance: Glomerular filtration is the main mechanism of renal excretion of GAB without significant contribution of Oct2 active transport.

1. Introduction

Gabapentin (GAB) is used to treat epilepsy, hot flashes, restless legs syndrome or neuropathic pain associated with cancer, postherpetic neuralgia or with diabetes [1–4]. GAB is not metabolized in rats or humans and the renal excretion is the main pathway of elimination [5]. Its renal excretion occurs by glomerular filtration and clinical data suggest the contribution by renal active secretion via organic cation transporter 2 (OCT2: humans; Oct2: rodents) [6–8]. However, drug-drug interactions and disease-drug interactions mediated by OCT2 were not extensively investigated for gabapentin up to date.

OCT2/Oct2 is expressed mainly in the kidneys, but it is also found in the placenta, thymus, adrenal gland and choroid plexus [9]. In mice, rats and humans, Oct2/OCT2 is expressed in the basolateral membrane of the proximal renal tubules [9–12]. This transporter plays a relevant role in the excretion of the endogenous substances dopamine, histamine, serotonin and drugs including, cetirizine, cimetidine, imipramine, lamivudine and cisplatin [9,12–14].

Cimetidine was characterized as an OCT2/Oct2 inhibitor drug by in vitro, in vivo, and clinical studies [8,10,14,15] and there are no differences between human and rats in terms of the affinity of cimetidine for OCT2/Oct2 [16]. Cimetidine is recommended as OCT2/Oct2 inhibitor by The International Transporter Consortium, which developed organograms for drug-drug interaction studies [17]. Therefore, the investigation of the potential GAB × cimetidine interaction will explain the impact of Oct2 activity on GAB pharmacokinetics.

Experimental *diabetes mellitus* (DM) is involved in several drug × disease interactions since it alters the gastrointestinal

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absorption, distribution, metabolism and renal excretion of drugs [18]. In terms of P450 enzymes activity, experimental DM suppresses the expression of the isoforms CYP 1A2, 2C11, 2C13 and 3A2 and induces the expression of CYP 2A1, 2B1, 2C12, 4A1 and 2E1 [13,19,20]. DM also influences the activity of phase II enzymes [13] and drug transporters. A reduction of 50–70% reduction in Oct2 levels was observed in rats with DM induced by streptozotocin [21,22].

Metformin is considered the drug of choice for the treatment of DM type 2, due not only to glycemic control, but also to beneficial contributions related to vascular complications, body weight, lipid profile, diastolic pressure and reduced mortality [23]. OCT2 significantly contributed to renal excretion of metformin, as evidenced in clinical [24] and in vitro studies [25,26]. However, the influence of metformin on GAB kinetic disposition was not previously investigated.

Considering the potential role of OCT2/Oct2 in GAB kinetic disposition and the related effects of experimental DM on the expression of Oct2, the aims of the present work were: 1) to characterize the potential of Oct2 inhibition by cimetidine on GAB pharmacokinetics; 2) to evaluate the role of experimental DM and the glycemic control by insulin treatment on GAB pharmacokinetics; 3) to evaluate the impact of metformin on GAB pharmacokinetics. Therefore, an experimental study was conducted in rats treated with a single dose of GAB. Plasma and urine drug concentrations were evaluated for pharmacokinetic analysis.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing approximately 250 ± 20 g (7–8 weeks) were obtained from the *Campus de Botucatu - Universidade Estadual Paulista* and housed in controlled environmental conditions (temperature of 20 ± 1 °C and humidity 60 ± 20%). The experimental protocols were approved by the Committee for Ethics in Animal Experimentation from the School of Pharmaceutical Sciences, UNESP, Araraquara, São Paulo (CEUA/FCF/Car n° 75/2015).

2.2. Induction of diabetes

Diabetes mellitus was induced in 14-h fasting animals by a single intravenous dose of 40 mg/kg streptozotocin (STZ, > 98%, Sigma Aldrich, St. Louis, MO, USA) dissolved in 0.1 M sodium citrate buffer (pH 4.5) [30]. Four days after STZ administration, animals were considered diabetic if the glycemia values without fasting were higher than 300 mg/dL [31]. All non-diabetic groups received a volume of 0.2 mL of 0.01 M citrate buffer solution pH 4.5 at the same time as administration of STZ in the diabetic groups as a control of the vehicle.

2.3. Experimental protocol

The experiment involved a total of 105 animals divided in five groups (vehicle + GAB, cimetidine + GAB, metformin + GAB, Experimental *diabetes mellitus* (DM) + GAB and DM + GAB + insulin). Serial blood samples and urine collection were required for pharmacokinetic analysis of GAB. To minimize the contamination of the urine with blood, animals were maintained singly in metabolic cages for urine sampling. Each group had 21 animals, of which 15 were used for blood and 6 for urine sampling, in order to achieve n = 6 per sampling time.

All animals received a single dose of 50 mg/kg GAB by gavage after 14-h fasting fifteen days after vehicle (citrate buffer) administration or diabetes confirmation. Cimetidine group received a single dose of 100 mg/kg cimetidine intraperitoneally, 60 min before receiving a single dose of GAB [14]. Metformin group animals receive a dose of 100 mg/kg metformin by gavage concomitantly with GAB dose [29]. Fifteen days after diabetes mellitus (DM) induction, DM + GAB group received 50 mg/kg GAB (gavage). DM + GAB + insulin group was treated with 2 UI NPH insulin twice daily for fifteen days after diabetes induction and then received 50 mg/kg GAB (gavage).

Blood samples were obtained through circumcision of 0.3 mm of the tail distal end, after local heating at 42 °C. Considering the total blood volume of animals and to avoid hypovolemic shock without fluid replacement, which could cause hemodilution [27,28], the maximum of five blood collections of 500 μL were drawn per animal. Individual blood samples were collected at times 0.25 h; 0.5 h; 0.75 h; 1 h; 2 h; 3 h; 4 h; 5 h; 6 h; 8 h; 10 h; 12 h after GAB administration, in heparinized tubes. Thus, sparse blood samples were collected at predefined times randomly combined to reach the sample size of 6 (n = 6), per sampling time. Urine samples were collected at time intervals 0–4 h; 4–8 h; 8–12 h. All samples were kept at −70 °C until analysis.

2.4. Analysis of GAB in plasma by HPLC-MS and in urine by HPLC-UV

The determination of GAB in rat plasma was performed by HPLC-MS (Perkin Elmer, Flexar SQ 300 MS, Shelton, USA). Phenacetin (Sigma-Aldrich, Missouri, USA) was used as internal standard (IS), at a concentration of 10 μg/mL in methanol. GAB and the IS were resolved on LiChrospher® C18 RP column (125 × 4.0 mm, 5 μm, Merck, Darmstadt, Germany) kept at 18 °C and mobile phase consisting of 5 mM ammonium acetate solution (pH = 4) and methanol (40:60, v/v) and flow rate of 0.4 mL/min [32] The mass spectrometry was performed on positive ion mode and the protonated molecular ions $[M\text{-}H]^+$ with *m/z* 172 and 180 were used for monitoring GAB and IS, respectively. The determination of GAB in rat urine was performed by HPLC-UV at λ = 360 nm. GAB and the IS (amlodipine besylate (99,7%, European pharmacopeia Reference Standard, Sigma-Aldrich, São Paulo) at a concentration of 200 μg/mL in water, were resolved in the same column, and the mobile phase consisting of 0.05 M sodium monobasic phosphate buffer (pH 3.9) and methanol (27:73, v/v), in a flow rate of 1.2 mL/min.

Shortly, 100 μL aliquots of plasma samples were added to 5 μL of IS solution (phenacetin), 50 mg of Na_2SO_4 and 1000 μL of dichloromethane:n-butanol (1:1, v/v) [33]. The microtubes were shaken and centrifuged (15 min, 15,000 × *g*) and 900 μL of the supernatant was separated and evaporated up to dryness. The residue was reconstituted in 120 μL of mobile phase and 10 μL was inject in the chromatographic system. Similarly, 100 μL aliquots of urine samples were added to 30 μL of IS solution (amlodipine), 50 mg of Na_2SO_4 and 1000 μL of dichloromethane:n-butanol (1:1, v/v). The microtubes were shaken and centrifuged (15 min, 15,000 × *g*) and 800 μL of the supernatant was separated and evaporated up to dryness. Aliquots of 40 μL of borate buffer (pH 8.2), 12 μL of derivatization agent FDNB 0.06 M and 400 μL of acetonitrile [34] were added to the residues. After homogenization, the microtubes were heated at 65 °C for 10 min for derivatization reaction. After cool, 10 μL of 1 M HCl were added and aliquots of 50 μL were injected in the system.

2.5. Pharmacokinetic and statistical analysis

The areas under the plasma concentration versus time curves in the interval zero to infinity ($AUC^{0-\infty}$) were calculated by Gauss-Laguerre Quadrature. The concentrations for the noncoincident times to the nodes of the quadrature were estimated by polynomial interpolation [35]. Differently from the trapezoidal rule, the Gauss-Laguerre Quadrature approach leads to more accurate results and its reliable in pharmacokinetics study designs when more than one sample (but not all of them) is taken from each animal [35,36]. The apparent total clearance (CL_T/F) was calculated using the equation $CL_T/F = Dose/AUC^{0-\infty}$. The maximum plasma concentrations (C_{max}) and the time to reach maximum plasma concentrations (T_{max}) were obtained from the observed data. Elimination half-life ($t_{½}$) was calculated by the equation: $t_{½} = (0.693 \times Vd)/Cl_T/F$, were Vd is the apparent volume of distribution calculated as C_{max}/dose. The fraction excreted unchanged in urine

(Fe) was calculated using the equation: concentration excreted unchanged in urine × urine volume (mL). The renal clearance (Cl_r) was calculated by: Fe × CL_T/F. The pharmacokinetic parameters were compared between groups using 95% confidence intervals. Variances were estimated considering that some blood samples were collected from the same animal, but not for all sampling times, thus considering a sparse sampling [36–38].

3. Results

The methods for determination of GAB in plasma and urine were linear in the intervals 0.6–30 μg/mL and 3–30 μg/mL, respectively. The relative standard deviation and the relative error of quality control samples did not exceed 15% for both biological matrices. GAB was determined in both plasma and urine samples up to 12 h after administration of 50 mg/kg in rats.

The STZ induced DM model resulted in only one rat that was not considered diabetic (glycemia values without fasting lower than 300 mg/dL). On following days after the STZ dose, diabetic animals presented the classical signs of diabetes such as a lower rate of weight gain, a higher consumption of water and higher diuresis when compared with other groups (data not shown).

The administration of a single dose of 50 mg/kg GAB in Wistar rats resulted in $AUC^{0-\infty}$, CL_T/F and $t_{1/2}$ values of 96.31 ± 12.28 μg·h/mL, 0.52 ± 0.07 L/h·kg and 2.72 ± 0.37 h, respectively. None of the animals presented ataxia or somnolence [38] after receiving 50 mg/kg GAB. The pharmacokinetic parameters $AUC^{0-\infty}$, T_{max}, C_{max}, Cl_T/F, $t_{1/2}$, Cl_r, and Fe were not changed after the administration of GAB and cimetidine or metformin (Figs. 1 and 2; Table 1).

The DM + GAB group resulted in higher Fe when compared to vehicle + GAB group: 0.83 ± 0.25 (0.62–1.04) × 0.48 ± 0.13 (0.38–0.58), respectively. DM + GAB + insulin also resulted in higher Fe (0.85 ± 0.10 [0.77–0.93]) and higher Cl_r when compared to vehicle + GAB group: 0.55 ± 0.10 (0.45–1.43) L/h·kg × 0.25 ± 0.07 (0.18–0.30) L/h·kg, respectively (Figs. 1 and 2; Table 1).

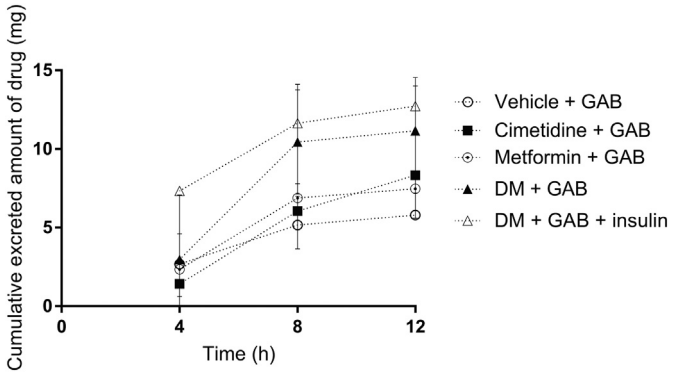

Fig. 2. Cumulative excreted amount of gabapentin (GAB) in urine (n = 6), per sampling interval. Vehicle + GAB group was treated with 50 mg/kg GAB by gavage; cimetidine + GAB group received 100 mg/kg cimetidine intraperitoneally 60 min before a single dose of 50 mg/kg GAB (gavage); metformin + GAB group was treated with 100 mg/kg metformin concomitantly with 50 mg/kg GAB (gavage). Fifteen days after diabetes mellitus (DM) induction, DM + GAB group received 50 mg/kg GAB (gavage); DM + GAB + insulin group was treated with 2 UI NPH insulin twice daily for fifteen days after diabetes induction and then received 50 mg/kg GAB (gavage).

4. Discussion

Several chromatographic methods for determination of GAB in biological fluids are described in the literature using high performance liquid chromatography with mass spectrometry, fluorescence or ultraviolet detection. Selective methods for determination of GAB in plasma and urine samples were validated with precision and accuracy at different concentration levels, no carry-over effect and acceptable stability of GAB in the tested conditions.

The present study describes the influence of cimetidine (Oct2 inhibitor), metformin (Oct2 substrate), DM and its glycemic control by insulin treatment on GAB kinetic disposition in male Wistar rats. The dose-independent PK parameters of GAB in vehicle + GAB group

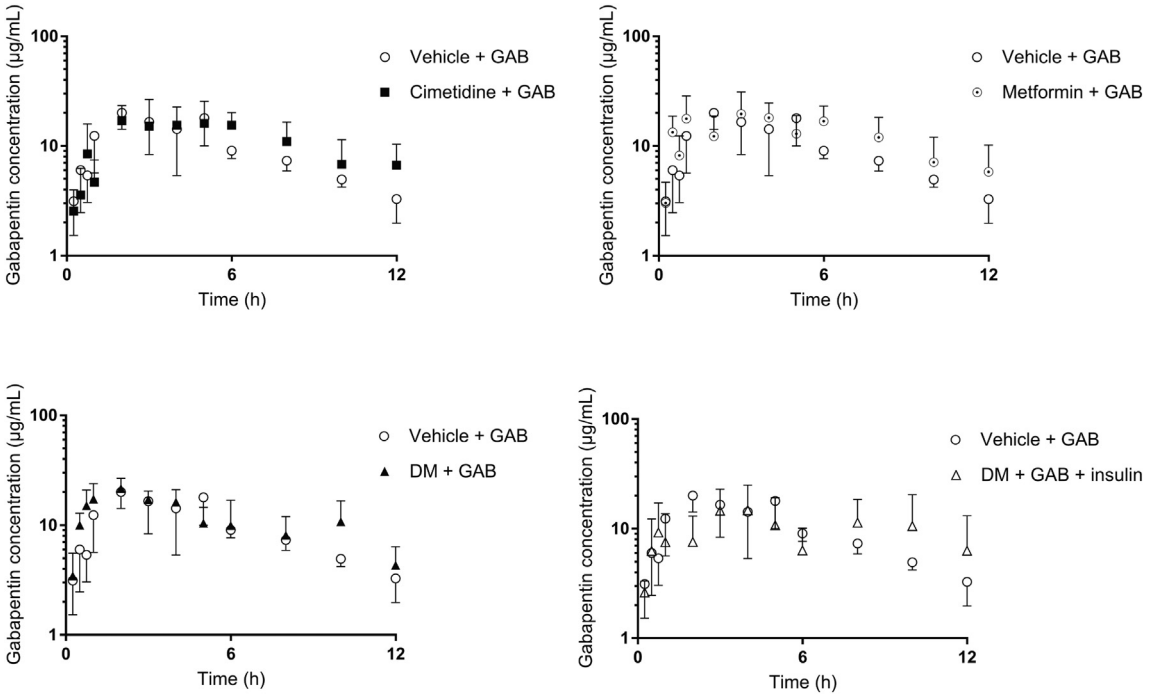

Fig. 1. Plasma concentration versus time curves of gabapentin (GAB) after single dose administration of 50 mg/kg (gavage) (n = 6 per sampling time). Vehicle + GAB group was treated with 50 mg/kg GAB by gavage; cimetidine + GAB group received 100 mg/kg cimetidine intraperitoneally 60 min before a single dose of 50 mg/kg GAB (gavage); metformin + GAB group was treated with 100 mg/kg metformin concomitantly with 50 mg/kg GAB (gavage). Fifteen days after diabetes mellitus (DM) induction, DM + GAB group received 50 mg/kg GAB (gavage); DM + GAB + insulin group was treated with 2 UI NPH insulin twice daily for fifteen days after diabetes induction and then received 50 mg/kg GAB (gavage).

Table 1
Pharmacokinetic parameters of gabapentin after single dose of 50 mg/kg (gavage). Data expressed as mean ± standard deviation (95% confidence interval).

	Vehicle + GAB	Cimetidine + GAB	Metformin + GAB	DM + GAB	DM + Insulin + GAB
$AUC^{0-\infty}$	96.31 ± 12.28	93.44 ± 27.48	110.55 ± 34.29	80.59 ± 41.73	110.90 ± 14.51
(μg·h/mL)	(86.48–106.13)	(71.46–115.42)	(47.21–113.97)	(83.16–137.97)	(99.29–122.51)
C_{max}	24.75 ± 9.26	26.26 ± 7.96	24.02 ± 4.11	29.52 ± 5.43	28.01 ± 7.70
(μg/mL)	(33.39–16.11)	(32.62–19.9)	(27.30–20.74)	(33.86–25.18)	(34.17–21.85)
T_{max} (h)	3.66 ± 1.11	4.16 ± 1.34	2.95 ± 1.49	2.95 ± 1.49	4.83 ± 2.27
	(2.77–4.54)	(3.08–5.23)	(1.25–3.32)	(1.75–4.14)	(3.01–6.64)
Cl_T/F	0.52 ± 0.07	0.54 ± 0.12	0.45 ± 0.17	0.62 ± 6.77	0.45 ± 0.07
(L/h·kg)	(0.46–0.57)	(0.44–0.63)	(0.31–0.58)	(−4.79–6.03)	(0.38–0.51)
$t_{1/2}$ (h)	2.72 ± 0.37	2.52 ± 0.22	2.87 ± 0.48	3.18 ± 0.83	1.99 ± 1.03
	(2.30–3.14)	(2.26–2.77)	(2.32–3.42)	(2.23–4.14)	(0.56–3.42)
Cl_r	0.25 ± 0.07	0.34 ± 0.10	0.36 ± 0.12	0.55 ± 0.10	0.27 ± 0.04
(L/h·kg)	(0.18–0.30)	(0.28–0.43)	(0.28–0.47)	(0.45–1.43)*	(0.24–0.30)
Fe	0.48 ± 0.13	0.64 ± 0.19	0.83 ± 0.25	0.85 ± 0.10	0.60 ± 0.07
	(0.38–0.58)	(0.51–0.80)	(0.62–1.04)*	(0.77–0.93)*	(0.13–0.53)

$AUC^{0-\infty}$: area under the plasma concentration versus time in the interval zero to infinity; **Cl_T/F**: apparent total clearance; **$t_{1/2}$**: elimination half-life; **Clr**: renal clearance; **C_{max}**: maximum plasma concentrations; **T_{max}**: times of maximum plasma concentrations; **Fe**: fraction excreted unchanged in urine.
* Statistical difference using 95% confidence intervals in relation to vehicle + GAB.

(Table 1) were similar to previous studies in rats treated with 10–200 mg/kg doses [39,40,41]. Although, no differences were observed between gender on concentration/dose ratio of gabapentin in humans [6,42], only male rats were investigated because the expression of rOCT2 mRNA and protein in the kidney of male rats were higher than those on females [43].

The pharmacokinetic parameters $AUC^{0-\infty}$, T_{max}, C_{max}, Cl_T/F, $t_{1,2}$, Cl_r, and Fe were not changed after the coadministration of GAB and cimetidine, a known Oct2 inhibitor [8,14,15,17] or the Oct2 substrate metformin [24,25]. Nadai et al., [14] used cimetidine to evaluate the contribution of Oct2 in the Cl_r of 3-methylxanthine and enprofylline in rats. The use of 50 mg/kg and 100 mg/kg cimetidine intravenously did not change the glomerular filtration rate, but resulted in lower renal clearance of 3-methylxanthine and enprofylline, respectively. Intravenous doses of 25 to 100 mg/kg of cimetidine increased the $AUC^{0-\infty}$ of guanfacine due to the reduced renal clearance in rats, which was attributed to the inhibition of renal tubular secretion mediated by Oct2 [15]. In a clinical study, Lal et al., [8] reported the interaction of GAB and cimetidine. Healthy volunteers were treated with daily doses of 1200 mg of GAB enacarbil, a pro-drug of GAB, and four doses of 400 mg of cimetidine for four days. Despite the decrease in Cl_r by cimetidine and the resulting increase of 24% in the area under the plasma concentration versus time curve in equilibrium-state (AUC_{SS}) of GAB, the authors suggest that these changes do not have any clinical relevance. The findings of our study corroborate the data observed [8], demonstrating that Oct2 inhibition by cimetidine does not significantly change the kinetic disposition of GAB.

Plasma blood glucose was measured in fasting and postprandial conditions in diabetic and nondiabetic rats. After 15 days of experiment, nondiabetic rats present fasting and postprandial glycemia values of 80–90 and 120–140 mg/dL, respectively. Diabetic animals (15 days post-STZ) usually have fasting and postprandial glycemia levels of 250–350 and 450–600 mg/dL, respectively. The impact of insulin on postprandial glycemia in diabetic animals is the normalization when 2IU/rat is administered two hours before blood collection with glycemia between 90 and 110 mg/dL. Due to the risk of hypoglycemia, insulin was not administered to nondiabetic animals. The impact of metformin on postprandial glycemia in diabetic animals is milder and it does not affect serum insulin concentration in nondiabetic rats [44]. Several investigations of drug-drug interaction have used metformin in nondiabetic animals [29,45,46], even as multiple doses [29].

Down-regulation of Oct2 has been reported in STZ induced DM in rats [21,22,47,48]. Considering the progress of diabetes as an important aspect, the decline of Oct2 expression was rapid after induction of diabetes with around 50% reduction after 7 days of diabetes in rats [22]. Although the STZ dose used in this study has been recognized as effective for DM establishment [30,49] no differences were observed in GAB kinetic disposition in plasma after 15 days after diabetes induction. The higher amount of GAB excreted unchanged in urine in diabetes does not seem to have any relevant impact on GAB systemic exposure. Therefore, the absence of differences in PK parameters between both cimetidine + GAB × vehicle + GAB and diabetes × vehicle + GAB suggests that Oct2 active transport is not relevant to GAB pharmacokinetics.

The increased Fe in DM + GAB and in DM + GAB + insulin groups and increased Cl_r between vehicle + GAB × DM + GAB + insulin could be explained by the glomerular hyperfiltration due the increased renal blood flow [50,51]. Phil et al. [51] investigated the renal hyperfiltration mechanisms in rats with DM and DM + insulin. The data showed that glomerular filtration and renal blood flow are enhanced in both groups. However, only in DM + insulin group a correlation between glomerular hyperfiltration and renal blood flow was observed (R^2: 0.81; $P < 0.0001$). This data corroborates the hypothesis that glomerular filtration is the major covariate on GAB kinetic disposition.

5. Conclusion

In summary, although Oct2 have been suggested to contribute to GAB renal excretion, our data shows that the Oct2 inhibitor cimetidine, the Oct2 substrate metformin and DM did not alter the kinetic disposition of GAB. Thus, the activity of Oct2 is not relevant to the kinetic disposition of GAB in rats and glomerular filtration is the main renal excretion mechanism enrolled on GAB elimination without significant contribution of active processes.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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