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Research Article

IMPACT OF ANTI-HYPERTENSIVE AGENT ON ANTI-DIABETIC DRUG IN DIABETIC AND NON-DIABETIC RATS – ASSESSMENT OF DRUG–DRUG INTERACTIONS

ANAND ARUMUGAM, VENKATA RAJESHAM V*

Department of Pharmacology, Bir Tikendrajit University, Canchipur, Manipur, India.
***Corresponding author: Venkata Rajesham V; Email: rajeshamvenkata@gmail.com**

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ABSTRACT

Objectives: The investigation was planned to evaluate pharmacokinetic and pharmacodynamic drug communication of Captopril and Metformin in healthy and diabetic albino Wistar rats succeeding single and many dosage treatments.

Methods: Therapeutic doses of captopril and metformin were administered to animal models, blood glucose levels were assessed by glucose oxidase-peroxidase (GOD-POD) method technique, and plasma captopril and metformin amounts were estimated by reversed-phase high-performance liquid chromatography (HPLC) technique to compute the pharmacokinetic attributes. In the present work, the pharmacokinetic and pharmacodynamic interaction between captopril and metformin was evaluated. Pre-clinical investigation might be supportive of evading drug–drug interactions in medical conditions. By means of HPLC, concentration versus time data were plotted for direct extraction of the pharmacokinetic attributes, peak plasma concentrations (C_{max}), and time to reach peak concentration (t_{max}). The linear trapezoidal rule was used in this work to compute AUC from 0 h to 24 h, which is denoted by $AUC_{0-t.}$

Results: In the determination of fasting serum glucose concentration in normal and streptozotocin-inducted diabetic animals on day 1 and day 8, there was a tremendous decline in the glucose levels in a significant manner (**p<0.001). When captopril alone administered group was compared to the group in combination with metformin on days 1 and 8, there was no significant variance in C_{max}, T_{max}, AUC_{o-t}, and $AUC_{o-inf.}$

Conclusion: The results concluded from the kinetic analysis revealed that there were no significant interactions in the kinetic parameters of metformin and captopril, both alone and in combination. However, further possible investigations are needed which might be helpful for diabetes.

Keywords: Captopril, Metformin, Drug interactions, Pharmacokinetic and pharmacodynamic interaction.

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INTRODUCTION

Hyperglycemia, or elevated blood glucose, is a hallmark of diabetes mellitus (DM), a long-lasting endocrine and metabolic condition caused through insufficient insulin secretion (or) action [1]. Millions of people are afflicted by DM now, and by 2030, that number is expected to triple, making DM a global problem. There have been reports of high diabetes-related morbidity (disease) and mortality (death) rates in the Nigerian population [2]. Type I diabetes is caused by insufficient insulin production by the pancreatic β-cells, whereas Type II diabetes is triggered by cells' inability to reply to insulin generated. High blood sugar, glucosuria, and a number of microvascular and macrovascular problems connected to endocrine and metabolic dysfunctions are phenotypical features of DM. The disease's classic symptoms are excessive thirst (polydipsia), frequent urine (polyuria), and hunger (polyphagia) [3].

A number of factors, including oxidative damage, inflammation, pancreatic beta cell death, and sustained elevations in vasopressin levels – which are secreted inside the hypothalamic supraoptic nucleus – have been implicated. Hyperglycemia-induced microvascular damage is one of the many consequences linked to determinedly high blood sugar points. This harm to the blood vessels has been connected to the stiffening of the blood vessels, which is primarily caused by an augmented construction of free radicals and a modified vascular immune system [4]. Surprisingly, oxidative stress caused by hyperglycemia is associated with difficulties in diabetes. This means that the body's natural anti-oxidant system may be overpowered. This is mostly caused by altered metabolism of lipids, proteins, and glucose, and a vicious development of reactive oxygen species [5].

Worldwide, the prevalence of both hypertension and DM is rising quickly, and among individuals with type 2 DM (T2DM), hypertension is a significant cardiovascular risk feature. A primary cause of death for T2DM patients is their significantly elevated (2-4-fold) hazard of cardiovascular disorders [6]. Among hypertensive patients, compensatory hyperinsulinemia and insulin resistance are also common findings. A grouping of anti-diabetic and anti-hypertensive medications is required and is being utilized more often meanwhile blood pressure-reducing therapy is crucial to lowering the hazard of emerging cardiovascular problems in T2DM suffering patients [7].

The oral biguanide antihyperglycemic drug metformin acts by causing a decline in hepatic glucose synthesis and raises skeletal muscle and hepatic insulin sensitivity without producing hypoglycemia [8]. Moreover, it also lowers high blood pressure and other cardiovascular illness consequences in people having T2DM. The pharmacological target location of metformin, the liver, is transported through an organic cation transporter (OCT1) in the sinusoidal membrane of liver cells, which is essential for metformin pharmacokinetics and pharmacodynamics [9]. The amount of metformin that inhibits the synthesis of glucose is dependent on its concentration in the liver. About 70% of metformin's renal excretion is mediated by OCT2, which is present in the basolateral membrane of renal-proximal tubules. Lactic acidosis may ensue from an intensification in systemic experience, or the plasma amount of metformin, brought on by reduced renal excretion of the drug due to renal OCT2 inhibition. According to earlier research, metformin inhibits P-glycoprotein and pregnane X receptor-controlled transactivation of cytochrome P450 (CYP) 3A4 gene. This suggests that metformin and verapamil may interact with one another through a PK-based drug–drug interface [10].

One of the main factors influencing morbidity and death in persons with Type 2 diabetes is cardiovascular disease (CVD) [11]. In this patient population, hypertension is related to an advanced occurrence of cardiovascular disease proceedings, as it coexists with diabetes in over 70% of cases. According to the United Kingdom Perspective Diabetes Study (UKPDS) results, lowering increased blood pressure may have a superior impact on reducing CVD morbidity and death than lowering hyperglycemia. In patients with cardiometabolic disorder, initiation of circulation and tissue renin-angiotensin systems plays a vital part in the development of insulin resistance and hypertension. There might be an enhancing action of angiotensin-converting enzyme (ACE) inhibitor on insulin, thus reducing the risk of CVD [12].

Captopril competitively inhibits the conversion of angiotensin I (ATI) into angiotensin II (ATII), which plays a vital part in the renin-angiotensin-aldosterone system (RAAS) as ATII has a direct effect on blood pressure. The ACE inhibitor captopril counteracts the RAAS's effects [13]. A homeostatic system which panels hemodynamic, water, and electrolyte equilibrium is RAAS. Renin is unrestricted by granular cells of the kidney's juxtaglomerular device post-sympathetic stimulation or after renal blood pressure or blood movement is decreased [14]. Renin converts circulating angiotensinogen to ATI in the bloodstream, and ACE before cleaves ATII from ATI. In terms of morbidity and mortality in diabetic patients with CVD, ACE inhibitors stand more effective than other antihypertensive drugs (such as calcium channel blockers). In current research, the influence of captopril on metformin was investigated in both normal and diabetic rat models.

METHODS

Animal preparation

Male Wistar rats (180–200 g) were designated from the CMR animal line, maintained under a controlled laboratory environment with a moistness of 50% and all rats were nourished with normal pellet food and water *ad libitum*. Protocol of animal was permitted by the institutional animal ethical committee (IAEC) bearing a reference number of 1447/PO/Re/S/11/CCSEA-100/A.

Induction of experimental diabetes

A 16-h fast was required of the male Wister albino rats (180–200 g) before they were given the useful agent streptozotocin (STZ) to induce Type-II DM. A closing dose of 60 mg/kg body weight was administered intraperitoneally to about 40 animals using 0.22–0.25 mL of a newly made STZ solution (60 mg/mL in 0.01 M citrate buffer; pH 4.5). The non-fasting blood glucose amount was measured 48 h post-STZ treatment to determine diabetes status in the rats. For this experiment, rats having blood glucose points >250 mg/dL were chosen [15]. Metformin (200 mg/kg) and captopril (12.5 mg/kg) were administered according to the doses in a single dose in the first two groups of diabetic rats individually and together in group IV. Furthermore, captopril was administered in healthy rats as a single dose.

Study design

Animals with diabetes were split into four groups, as divided in the following pattern, consisting of six animals each (n=6).

Grouping of rats

I : Metformin (200 mg/kg)
II : Captopril (12.5 mg/kg)
III : Captopril
IV : Metformin and Captopril

Blood sample collection

Following drug delivery, capillary tubes were used to extract 0.5 mL of blood from the retro-orbital plexus of individually anesthetized (isoflurane) rats at pre-arranged intermissions. Samples were placed into Eppendorf tubes that were labeled beforehand and included 10% K2EDTA anticoagulant (20 µL). Samples were taken at intervals of 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, and 24 h (post-dose). A constant volume of saline is given to substitute blood bulk at each blood extraction time [16].

Blood samples were centrifuged using a cooled centrifuge (REMI ULTRA) at 3000 rpm for 5 min to obtain plasma. After obtaining plasma samples, they were placed in microcentrifuge tubes that had already been labeled and kept at −30°C till pharmacokinetic and pharmacodynamic attributes were bioanalyzed. As previously mentioned, on day 8, every procedure was also carried out. Using WinNonlin® 5.1 software, a non-compartmental study was utilized to calculate pharmacokinetic attributes. Concentrations derived from the bio-analytical technique mentioned above were collated [17].

Chromatographic associates

The Shimadzu liquid chromatographic apparatus manufactured by Shimadzu Corporation, Tokyo, Japan, comprised a Pump model (LC-20 AT VP), with a Detector model (SPD-20AV), and a Rheodyne manual injector equipped with a 20 µL loop. Using PurospherÒ Star RP-18 end-capped analytical column (25 cm × 4.6 mm), chromatographic separation was achieved. To determine data demand analysis, a GC-10 program was utilized.

The mobile phase was acetonitrile to water 50:50 (v/v), and the diluent was acetonitrile to water 60:40 (v/v). A pH was then corrected to 3.0 using phosphoric acid (85%). The mobile phase was vented in an ultrasonic bath and filtered over a 0.45 µl filter before being delivered into the system. With a detecting wavelength of 218 nm and flow pace of 1.0 mL/min at room heat, isocratic circumstances were used. An internal standard of caffeine was employed [18].

Preparation of plasma sample for high-performance liquid chromatography (HPLC) study

To prepare rat plasma (0.5 mL) trials for chromatography, 2.5 mL of ice-cold 100% ethanol was used to precipitate proteins for each 0.5 mL of plasma. Ethanol was placed into a fresh tube following centrifugation. Post-vortexing for 1 min, the precipitate was resuspended with 1mL of acetonitrile. Following centrifugation (5000–6000 rpm; 10 min), acetonitrile was added to ethanol, and room-temperature nitrogen steam was used to almost completely dry the organic mixture. For HPLC analysis, samples were reconstructed in 200 µL of acetonitrile (70%) with water (30%) inserted [19].

Pharmacokinetic study

Concentration time data were plotted with peak plasma concentrations (C_{max}) and the time to reach peak concentration (t_{max}). The linear trapezoidal regulation was used in this work to compute the AUC from 0 h to 24 h, which was denoted by AUC_{0-t}, whereas AUC from 0 h to infinity was denoted by $AUC_{0-\alpha}$.

Formula AUC_{0-t} + [Clast/K]; Clast: concentration in µg/ml at final time point; K: elimination rate constant for $AUC_{0-\alpha}$, number of pharmacokinetic variables, including elimination half-life (t1/2) and area under the curve (AUC). For every subject, the following equations are used to calculate the volume of distribution (V/f), total clearance (Cl/f), and mean residence time by the non-compartmental pharmacokinetic tool called RAMKIN [20].

Half-Life [t ½]

The amount of time needed for a medicine to decrease its concentration in the body by 50% is known as its half-life. If the elimination is a first-order process, it can be computed using the elimination rate constant.

$$t½ = 0.693/K$$

Where K is the elimination rate constant.

AUC

A drug's bioavailability was represented as AUC stretched to an indefinite duration. Linear trapezoidal rule was used to calculate it from 0 h to the final sample time, t.

For the remaining area (Wagner's approximation).

Table 1: Plasma concentration (ng/mL) in diabetic rats with drug treatment

Time (hours)	Metformin alone		Metformin combination with Captopril	
	(day 1)	(day 8)	(day 1)	(day 8)
0	0±0	25.21±0.65	0±0	26.82±0.43
0.5	126.34±0.5	129.76±0.25	129.86±0.7	134.27±0.76
1	245.54±0.87**	278.96±0.84**	258.63±0.6**	286.27±0.86**
2	325.19±0.16**	362.27±0.93**	342.46±0.3**	389.26±0.85**
4	267.76±0.43**	287.26±0.36**	285.25±0.8**	301.73±0.46**
6	132.35±0.69**	146.25±0.34**	146.95±0.7**	159.47±0.35**
8	54.36±0.75**	105.85±0.32**	64.25±0.43**	115.25±0.73**
24	0±0	46.26±0.87**	0±0	57.45±0.64

Values were represented in Mean±SEM. **p<0.001 was measured as substantial, compared to the values on the 1st and 8th day

$$\therefore \text{The total AUC}_{0-\alpha} = \text{AUC}_{0-t} + \text{AUC}_{t-\alpha}$$
$$= \text{AUE}_{0-t} + C_{(t)}/K$$

$C_{(t)}$ represents the concentration at the last time slot.

Pharmacodynamic study

On the 1st day of each group, pharmacodynamic measurements were made. Blood samples were then taken, and the dose was continued until the 8th day, as well as a rough estimate for blood glucose [21].

Statistical analysis

Data were described as Mean±Standard error of the mean. Statistical comparisons were made using Student's paired t-test, $p<0.05$ was measured to assess the significance.

RESULTS

In this investigation, the rats were given their respective doses accordingly for a period of 8 days, and concentrations of metformin individually and in combination with captopril were estimated in the plasma in ng/mL. When the concentrations of metformin alone were compared on the 1st and 8th day of treatment, there was a significant (**p<0.001) reduction in plasma glucose levels gradually in 24 hours (Table 1). Similarly, the combination of metformin and captopril also produced same result and was shown in Fig. 1.

When the plasma levels (ng/mL) of captopril in healthy and diabetic rats were compared there was no significant variation observed (Table 2) on days 1 and 8. Similarly, when the plasma levels of captopril alone and captopril in combination with metformin were compared, there was no significant difference observed on days 1 and 8 (Table 3 and Fig. 2). The concentrations of glucose in normal and STZ treated diabetic rats were estimated on day 1 & 8, and was found that there was significant reduction in serum glucose levels (**p<0.01) with metformin alone and metformin along with captopril treated rats (Table 7 and Fig. 4).

Values were represented in Mean±Standard error of the mean. ^{ns}p was considered non-significant.

Pharmacokinetic attributes of metformin single and in mixture with captopril on days 1 and 8 were compared. It was observed that there was no significant variance noticed in C_{max}, T_{max}, AUC_{o-t}, and AUC_{o-inf} in both groups (Table 4). Similarly, when there was a comparison of pharmacokinetic attributes in a group treated with captopril in healthy and diabetic rats, there was no significant difference noticeable (Table 5).

When the captopril-alone administered group was compared to the group in a mixture with metformin on days 1 and 8, there was no significant variance in C_{max}, T_{max}, AUC_{o-t}, and $AUC_{o-inf.}$ (Table 6 and Fig. 3).

In the normal and STZ-persuaded diabetic rats the fasting concentrations of glucose in serum on day 1 and day 8, there was a tremendous decline in the glucose levels in a significant manner (**p<0.01).

Table 2: Plasma points (ng/mL) of Captopril in normal and diabetic rats

Time (hours)	Captopril in healthy Rats		Captopril in Diabetic Rats	
	Day 1	Day 8	Day 1	Day 8
0	0±0	5.65±1.32	0±0	7.85±1.43
0.5	28.43±4.53	31.65±4.53	27.65±2.53^{ns}	33.63±2.74^{ns}
1	45.53±3.65	49.37±3.65	44.87±3.75^{ns}	53.83±3.92^{ns}
2	32.25±4.64	36.86±4.64	35.95±4.62^{ns}	38.52±4.27^{ns}
4	21.42±4.85	25.38±4.85	25.38±3.64^{ns}	27.83±3.53^{ns}
6	11.64±2.63	19.64±2.63	13.27±2.54^{ns}	17.26±2.36^{ns}
8	0±0	15.96±2.53	0±0	12.72±2.53^{ns}
24	0±0	8.64±2.62	0±0	9.38±2.52^{ns}

Values were represented in Mean±Standard error of the mean. ^{ns}p was considered non-significant

Table 3: Plasma points (ng/mL) of captopril single and with metformin in diabetic rats

Time (hours)	Captopril alone		Captopril with Metformin	
	Day 1	Day 8	Day 1	Day 8
0	0±0	7.85±1.43	0±0	9.32±2.53
0.5	27.65±1.53	33.63±1.74	26.32±1.57	31.54±1.25
1	44.87±1.75	53.83±1.92^{ns}	42.54±1.48	50.42±1.63^{ns}
2	35.95±0.62	38.52±0.27^{ns}	37.87±0.37	35.42±0.53^{ns}
4	25.38±1.64	27.83±1.53^{ns}	29.26±1.64	29.63±1.73^{ns}
6	13.27±1.54	17.26±1.36^{ns}	15.74±1.42	19.42±1.42^{ns}
8	0±0	12.72±1.53^{ns}	0±0	16.32±1.21^{ns}
24	0±0	9.38±1.52^{ns}	0±0	10.42±1.74^{ns}

Values were represented in Mean±Standard error of the mean. **p<0.001 was measured as substantial, compared to the values on 1st and 8th day

DISCUSSION

Given the frequency, morbidity, and mortality related to the combination of such conditions, and frequent difficulty in treatment, hypertension in diabetics is a significant health issue. Those with diabetes likely have a 1.5–2 times greater prevalence of hypertension than the overall population. Thus, lowering cardiovascular risk should come first in the treatment of diabetes [22]. One component of insulin resistance or metabolic disease that carries a notably elevated hazard of cardiovascular demise, is microalbuminuria, a substantial forecaster of cardiovascular proceedings.

A variety of antihypertensive medication classes, including ACE inhibitors, calcium channel blockers, thiazide diuretics, and angiotensin-II type 1 receptor blockers (ARBs), are frequently utilized to control blood pressure in diabetics. Cheung provided evidence that people with diabetes who are hypertensive have been using calcium antagonists frequently. The likelihood of acquiring diabetes was considerably decreased using the calcium channel blocker verapamil [23].

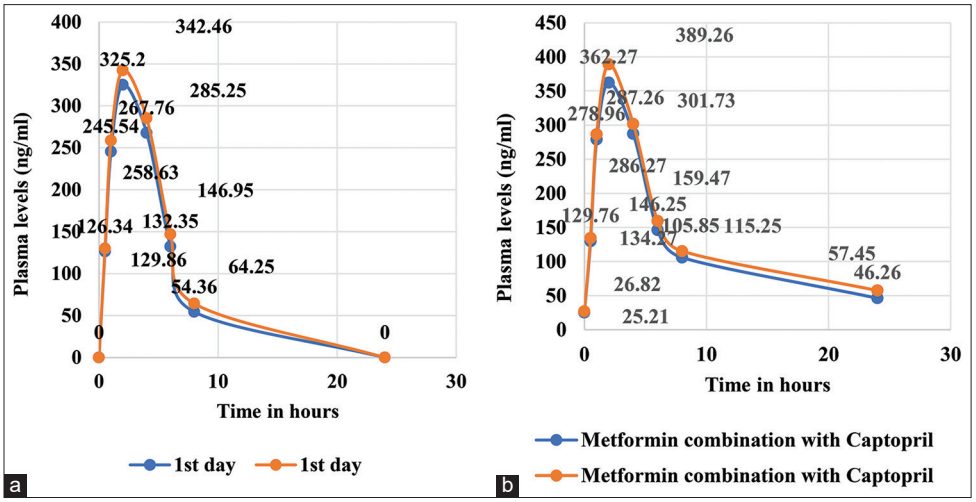

Fig. 1: (a and b) Plasma concentration (ng/mL) in diabetic rats with drug treatment

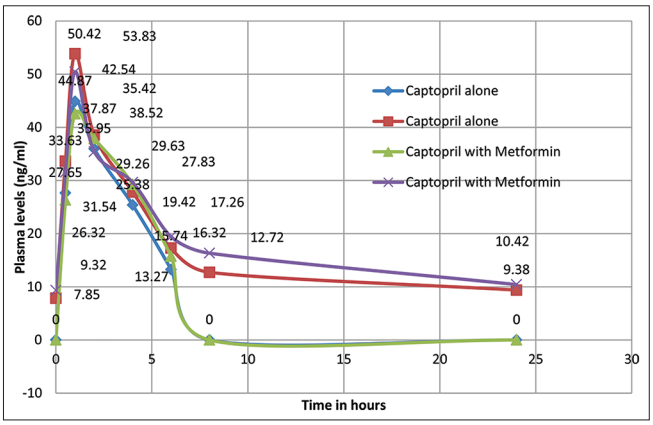

Fig. 2: Plasma points (ng/mL) of captopril single and with metformin in diabetic rats

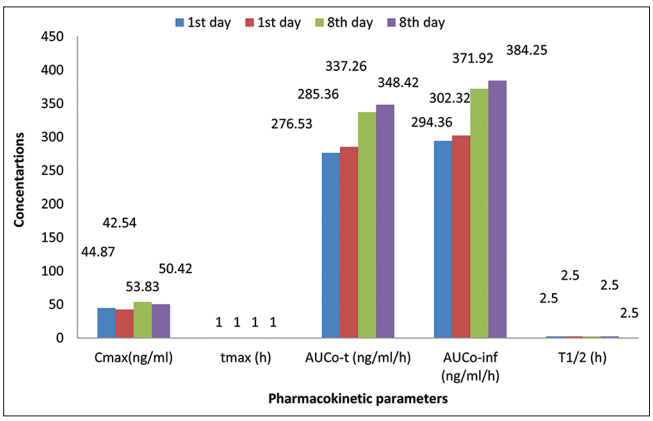

Fig. 3: Pharmacokinetic attributes of single captopril and blend of metformin day 1 and 8

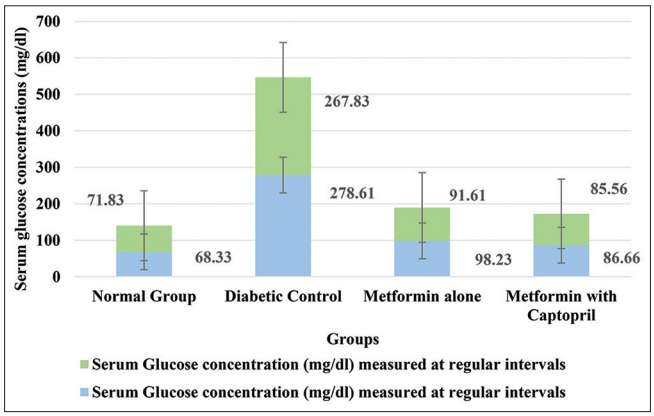

Fig. 4: Concentrations of glucose in normal and streptozotocin persuaded diabetic rats

In a similar vein, antihypertensive and antidiabetic medications are frequently taken together by diabetes patients. ARB treatment for diabetic and hypertension patients improved microvascular and macrovascular changes. To effectively manage T2DM and address concurrent pathologies, collective pharmacological treatment typically involves meticulous consideration of drug–drug interactions when using antihyperglycemic medications. A study by Mitra *et al*. investigated the relationship between diabecon (D-400), a herbo-mineral anti-diabetic agent with other medications. The primary goal of the current study was to evaluate drug interactions between captopril, enalapril, and lisinopril by the regularly given antidiabetic medications glimepiride, pioglitazone, and glibenclamide using HPLC [24].

Type 2 diabetes and hypertension commonly coexist as concurrent conditions. Individuals with diabetes exhibit a prevalence of hypertension that is double that of those without the condition. Moreover, individuals with hypertension often exhibit indicators of resistance to insulin and have an increased propensity to develop diabetes compared to those with normotension. Heart disease is the leading cause of mortality and morbidity among those with diabetes, exacerbated by hypertension [25].

Given the frequency, serious morbidity and mortality, and often challenging treatment of this mix of conditions, hypertension in diabetics is a significant health concern. Those with diabetes likely have a 1.5–2 times greater prevalence of hypertension than the overall population. Thus, lowering cardiovascular risk should come first while managing diabetes [26].

Drugs are used in the prevention and treatment of symptoms and illnesses, yet one of the primary problems with combination therapy is drug-drug interactions. Patients with diabetes often receive treatment for their blood pressure using beta-blockers and other hypertensive medications. Thus, monitoring, minimizing, and controlling drug interactions between antihypertensive and antidiabetic medications must be initiated. Patients with cardiovascular disease, collagen vascular disease, and mild to moderately severe hypertension can benefit from ACE inhibitors [27]. Additionally, patients with cardiovascular

Table 4: Pharmacokinetic attributes of metformin single and mixture with captopril on days 1 and 8

Pharmacokinetic attributes	1st day		8th day	
	Metformin	Metformin blend with Captopril	Metformin	Metformin blend with Captopril
C_{max} (ng/mL)	325.19±18.16	342.46±15.3^{ns}	362.27±18.93	389.26±15.85^{ns}
t_{max} (h)	2.00±0.23	2.00±0.46^{ns}	2.00±0.23	2.00±0.36^{ns}
AUC_{o-t} (ng/mL/h)	1353.68±23.74	1398.74±27.85^{ns}	1892.74±35.47	1912.26±56.62^{ns}
AUC_{o-inf} (ng/mL/h)	1543.94±35.74	1579.52±36.85^{ns}	2043.63±63.73	2197.37±38.93^{ns}
$T_{1/2}$ (h)	4.25±0.42	4.74±0.28^{ns}	4.52±0.78	4.52±0.93^{ns}

Values were represented in Mean±Standard error of the mean. nswas considered non-significant, compared to the values on the 1st and 8th day

Table 5: Pharmacokinetic attributes of single captopril in healthy and diabetic rats

Pharmacokinetic attributes	1st day		8th day	
	Captopril in healthy rats	Captopril in diabetic rats	Captopril in healthy rats	Captopril in Diabetic rats
C_{max} (ng/mL)	45.53±3.65	44.87±3.75^{ns}	49.37±3.65	53.83±3.92^{ns}
t_{max} (h)	1.00±0.43	1.00±0.53^{ns}	1.00±0.12	1.00±0.24^{ns}
AUC_{o-t} (ng/mL/h)	267.63±13.83	276.53±15.84^{ns}	326.36±35.74	337.26±24.84^{ns}
AUC_{o-inf} (ng/mL/h)	288.24±17.83	294.36±14.74^{ns}	359.74±24.85	371.92±31.42^{ns}
$T_{1/2}$ (h)	2.5±0.36	2.5±0.64^{ns}	2.5±0.42	2.5±0.26^{ns}

Values were represented in Mean±Standard error of the mean. ns was considered non-significant, compared to the values on the 1st and 8th day

Table 6: Pharmacokinetic attributes of single captopril alone and blend with metformin day 1 and 8

Pharmacokinetic attributes	1st day		8th day	
	Captopril alone	Captopril in combination with Metformin	Captopril alone	Captopril in combination with Metformin
C_{max} (ng/mL)	44.87±3.75	42.54±7.48^{ns}	53.83±3.92	50.42±6.63^{ns}
t_{max} (h)	1.00±0.53	1.00±0.74^{ns}	1.00±0.24	1.00±0.63^{ns}
AUC_{o-t} (ng/mL/h)	276.53±15.84	285.36±14.85^{ns}	337.26±24.84	348.42±24.73^{ns}
AUC_{o-inf} (ng/mL/h)	294.36±14.74	302.32±16.83^{ns}	371.92±31.42	384.25±21.43^{ns}
$T_{1/2}$ (h)	2.5±0.64	2.5±0.27^{ns}	2.5±0.26	2.5±0.52^{ns}

Values were represented in Mean±Standard error of the mean. nswas considered non-significant, compared to the values on the 1st and 8th day

Table 7: Concentrations of glucose in normal and STZ-persuaded diabetic rats

Treatment	Serum glucose concentration (mg/dL)	
	Day 1	Day 8
Normal group	68.33±2.4	71.83±2.8
Diabetic control	278.61±6.64**	267.83±2.17**
Metformin alone	98.23±3.09**	91.61±1.34**
Metformin with captopril	86.66±2.69**	85.56±1.63**

Values were expressed in Mean±Standard error of the mean. **p<0.01; **p<0.05 vs. Normal; **p<0.01 vs. Diabetic Control. STX: Streptozotocin

diseases can rely on multiple medications, but get envisaged with the possible drug-drug interactions. This is because the administration of multiple medications together can have a substantial impact on a drug's availability [28]. In the current investigation, the interactions between commonly prescribed and co-administered medications and ACE inhibitors (enalapril, captopril, and lisinopril) in conditions that mimicked the human body were examined.

In the pharmacokinetic studies of metformin and captopril, the concentrations of metformin alone and in combination with captopril were analyzed. It was experimental that there was a noteworthy down in the concentrations of metformin which was evidenced by the values [29]. Adding on, the levels of captopril in healthy and diabetic rat models showed no substantial variation in concentrations of captopril. As captopril alone and in combination with metformin when administered to diabetic rat models, there was no substantial difference in plasma concentrations of captopril. Pharmacokinetic attributes such as C_{max}, T_{max}, AUC, and $t_{1/2}$ in the above comparisons were also noticed, not any type of significant contrast was observed. Drugs were analyzed in this study using the AUC method. Interacting results reveal that no notable changes in availability or retention times were noticed. Nevertheless, the HPLC data did not reveal any appreciable variation in the percentage of both medications that were available, indicating that there was no interaction.

This study analyzed medicines by assessing AUC; the results indicate no significant variations in availability and no changes in retention duration were identified. Nevertheless, the results indicated that no interaction since HPLC analysis showed no significant alteration in the percentage availabilities of either drug.

When the pharmacodynamic parameter – fasting blood glucose levels were compared between metformin and in combination with captopril, the concentrations of blood glucose levels were under control. This study indicated that the influence/impact of captopril on the concentration of metformin levels might not be attributed to a significant effect that can lead to a drug–drug interaction.

CONCLUSION

The current investigation indicated that the kinetic analysis revealed that there were no significant interactions in the kinetic parameters of metformin and captopril, both alone and in combination when administered as a single dosage to diabetic rats. In addition, the interaction between metformin and captopril produced significant

effects. Furthermore, the development of the HPLC method indicated that simultaneous detection of plasma concentrations of metformin and captopril is feasible. Thus, it may be concluded that concurrent use of these two medications might be effective in the control of diabetes. In addition, combination therapy may be safe and very helpful for diabetics because of their low pharmacokinetic interaction.

AUTHOR'S CONTRIBUTIONS

A.A.: Conceptualization, Methodology, Investigation, Preparation of original Draft. V.R.V.: Project administration, review, and final approval. The authors have read and agreed to the published version of the manuscript.

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Nil.

CONFLICTS OF INTEREST

The authors express no conflicts of interest.

ETHICS APPROVAL

All the participants expressed their consent to participation. IAEC has approved the protocol with reference number 1447/PO/Re/S/11/CCSEA-100/A.

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