Advances in Bioresearch
Adv. Biores., Vol 15 (5) November 2024: 36-46

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.15.6.3646

Advances in Bioresearch

ORIGINAL ARTICLE

Pharmacokinetic and Pharmacodynamic Drug- Drug Interactions between Anti-Hypertensive & Anti-Diabetic Drug in Normal And Diabetes Induced Rats

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ABSTRACT
The objective of the study was to examine the pharmacokinetic and pharmacodynamic interactions of captopril and glyburide following single and multiple doses in both healthy and diabetic Wistar rats. Animals received therapeutic dosages of captopril and glyburide. Blood glucose levels were assessed with the GOD/POD method, while plasma concentrations of captopril and glyburide were quantified using a highly sensitive RP-HPLC technique, and pharmacokinetic characteristics were determined. In the single-dose research, the reduction in blood glucose and metformin concentrations was substantially more pronounced in rats administered both glyburide and captopril than in those treated with glyburide alone. This interaction may result from captopril inhibiting P-glycoprotein-mediated transport of glyburide. The current investigation observed pharmacokinetic and pharmacodynamic interactions between captopril and glyburide. Both P-glycoprotein and cytochrome P450 enzymes are implicated in the potential interaction.
Key words: *Captopril, Glyburide, RP-HPLC, P-glycoprotein and CYP enzymes*

Received 15.09.2024 Revised 02.10.2024 Accepted 25.11.2024

How to cite this article:
Anand A, V. Venkata Rajesham. Pharmacokinetic and Pharmacodynamic Drug- Drug Interactions between Anti-Hypertensive & Anti-Diabetic Drug in Normal and Diabetes Induced Rats. Adv. Biores. Vol 15 [6] November 2024. 36-46

INTRODUCTION

Drug interactions constitute a major and prevalent source of pharmaceutical mistakes. Approximately 6-30% of all adverse medication responses result from drug interactions. Adverse medication interactions occur in 2.2-30% of hospitalized patients and 9.2-70.3% of outpatients [1]. A drug-to-drug interface is alteration of the impact of a single drug (target drug) due to prior or concurrent administration of another drug [2]. Drug interactions pose significant risks for patients concurrently using numerous drugs, as such interactions elevate the likelihood of health complications, including hospitalization [3]. Drug interactions can modify the therapeutic efficacy of medications, induce toxicity, or unexpectedly enhance pharmacological activity. The prevalence of drug interactions is a worldwide issue that is escalating swiftly due to the rising number of patients and medications [4]. Hypertension in diabetic people is a prevalent and serious health issue that is frequently challenging to manage and results in considerable morbidity and mortality. Hypertension is likely 1.5 to 2 times more prevalent in diabetes patients compared to the general population [5]. The concurrent existence of hypertension and diabetes impacts the same principal target organs, leading to left ventricular hypertrophy, coronary artery disease, compromised renal function, the onset of diabetic retinopathy, and the emergence of cerebral disease [6]. The antihypertensive efficacy of ACE inhibitors diminishes when co-administered with nonsteroidal anti-inflammatory medications [7]. This impact is amplified by calcium channel blockers [8] and beta-blockers

[9]. Agranulocytopenia arises following the concurrent treatment of ACE inhibitors and interferon [10], while nitritoid responses manifest with the coadministration of gold salts & ACE linked inhibitors [11]. Cytokine negate the antihypertensive efficacy of ACE linked inhibitors [12]. Potassium-depleting diuretics induce significant hypokalemia [13], while potassium-sparing diuretics result in hyperkalemia [14-16]. ACE inhibitors may elevate potassium levels in the body [17,18]. Alpha-blockers augment the antihypertensive efficacy of ACE linked inhibitors [19]. Iron subjunction effectively alleviates coughing produced by ACE linked inhibitors [20] & may hinder absorption of ACE linked inhibitors [21]. The low glycemic impact got augmented by antidiabetic medications and insulin [22, 23]. The simultaneous administration of azathioprine and ACE inhibitors is linked to anemia [24]. Patients administered general anesthetics and ACE inhibitors frequently experience substantial hypotension [25]. The dual use of ACE inhibitors and immunosuppressants elevates the risk of bone marrow suppression in patients. Hypertension in diabetic individuals is a serious health issue due to the prevalence of this comorbidity, its association with considerable morbidity and mortality, and the challenges it presents in treatment. The incidence of hypertension among diabetes patients is likely 1.5 to 2 times greater to that in universal population [26]. Mitigating cardio vascular hazard is hence paramount objective in managing of diabetes. Microalbuminuria is a significant forecaster of cardio vascular actions & constitutes one of elements of insulin resistance condition, that poses an elevated risk of cardiovascular mortality [27]. Various categories of antihypertensive medications can be employed to regulate blood pressure in individuals with diabetes. Angiotensin II type 1 receptor blocker (ARB), calcium channel blocker (CCB), thiazide diuretic, & angiotensin-converting enzyme (ACE) inhibitor gor prevalent [28].

Glyburide is utilized for the management of type II diabetes, in combination with dietary modifications, physical action, & occasionally additional pharmacological agents. Glyburide is classified as a sulfonylurea medication. Glyburide decreases glucose level by increasing pancreatic insulin production & enhancing the body's insulin use efficiency. This medication solely aids in reducing blood glucose levels in those whose bodies inherently generate insulin. Glyburide is not indicated for the management of type I diabetes, an ailment considered by body's incapability to make insulin, nor for diabetic ketoacidosis, a severe complication arising from untreated hyperglycemia.

Captopril is powerful viable inhibitor of angiotensin-converting enzyme (ACE), which catalyzes the conversion of angiotensin I (ATI) to angiotensin II (ATII). Angiotensin II controls blood pressure & a crucial element of renin-angiotensin-aldosterone system (RAAS). Captopril, an ACE inhibitor, mitigates the effects of the RAAS, a homeostatic system that regulates hemodynamics, as well as fluid and electrolyte equilibrium. Renin is secreted by the granule cells of juxtaglomerular device in kidney in response to sympathetic nerve stimulation or a decrease in renal blood pressure/flow. Renin in bloodstream cuts mixing angiotensinogen to ATI that is subsequently slashed by AT-converting enzyme to angiotensin II. ACE inhibitors have demonstrated superior efficacy compared to other antihypertensive representatives, like CCB, in decreasing cardiovascular morbidity and death among hypertensive diabetic patients. The research is meant to observe pharmacokinetic & pharmacodynamic interactions between the antihypertensive agent captopril and the antidiabetic agent glyburide in both normal and diabetic-induced rat models.

MATERIAL AND METHODS

Preparation of Animal

Male Wistar rat models (180 and 200 grams), were used in the present study. Each rat was housed in a regulated laboratory setting with humidity sustained at 50%. They received a regular pellet diet and unrestricted access to water. The animal study procedure received consent from Institutional Animal Ethics Committee with reference no: 1447/PO/Re/S/11/CCSEA-100/A.

Initiation of Experimental Diabetes

Animals were given streptozotocin (STZ), a pharmacological matter effective in developing type I diabetes, to induce diabetes. Forty-five animals were administered an intraperitoneal injection of 0.22 to 0.25 ml of recently made STZ solution (60mg per ml in 0.01M citrate buffer with pH 4.5), achieving an ultimate dosage of 60mg per kg weight. Disease status got evaluated in STZ-treated rat models by monitoring non-fasting blood sugar levels post 48 hours.

Rat models exhibiting serum sugar levels over 300mg per dL got selected for the investigation. The study, as previously described, involved categorizing animals with elevated hyperlipidemia into six distinct categories. A separate cohort of normal animals was preserved as non-hyperlipidemic, with each group including six animals. An open parallel study design was employed [18].

Rat models groups

I : Glyburide (5mg/kg) in unit dose / day in diabetic rat models.

III : Captopril (12.5mg/kg) in unit dose / day in diabetic rat models.
IV : Captopril in unit dose / day in normal rat models
V : Glyburide & Captopril associated intake as a unit dose / day in diabetic rat models.

Blood Sample assembly

Following drug delivery, 0.5 ml blood samples obtained through the retroorbital plexus of each anesthetized model (isoflurane) at designated time intervals and transferred into an early-labeled Eppendorf tube having 10% K2EDTA anticoagulant (20µl) via a capillary tube. Sampling intervals included 0 (before-dose), 0.5, 1, 2, 4, 6, 8, & 24 hours (after-dose).

At each blood draw, an equivalent capacity of saline got infused to compensate for the blood volume. Plasma was extracted by centrifuging the blood samples at 3000rpm for 5 minutes in a chilled centrifuge (REMI ULTRA). The collected plasma sample got were place to before-labeled microcentrifuge tube & kept at -30°C until bioanalysis for pharmacokinetic & pharmacodynamic characteristics. All events got executed on day 8 as previously outlined. Pharmacokinetic parameters were determined using non-compartmental investigation utilizing WinNonlin®5.1software. The concentration derived from aforementioned bio-analytical procedures got summarized. [29, 30]

Chromatographic state

Shimadzu liquid chromatographic arrangement from Shimadzu Corporation, Japan, comprised a Pump (LC-20 AT VP), a Detector (SPD-20AV), and a Rheodyne injector equipped with 20µL circle. Chromatographic separation got achieved utilizing a PurospherÒ Star RP-18 end-capped analytical column (25cm×4.6mm id). The GC-10 software got utilized for data request.

Acetonitrile:water (50:50; v/v), with pH accustomed to 3.0 using 85% phosphoric acid, served as the mobile phase, while acetonitrile:water (60:40; v/v) got utilized as the dilutant. Prior to introduction into system, the mobile phase got sifted over a 0.45µm filter & vented utilizing a bath (ultrasonic). Isocratic settings got employed with a flow pace of 1.0mL per min at ambient heat, having a detection wavelength of 254 nm. Hydrochlorothiazide served as the internal standard.

Preparation of Plasma Samples for HPLC Analysis

Plasma samples (0.5 ml) got prepared for chromatography by precipitating proteins by 2.5ml of ice cold 100% ethanol for every 0.5ml of plasma. Following centrifugation, ethanol got shifted to sterile tube. Precipitate got resuspended in 1mL of acetonitrile and vortexed for a minute. Following centrifugation at 5000 to 6000 rpm for 10 minutes, acetonitrile got introduced to ethanol, & organic mixture got almost evaporated at ambient temperature using nitrogen gas. Samples got reconstituted in 200µL of acetonitrile (70%) & water (30%), which got subsequently injected in for HPLC analysis.

Pharmacokinetic Investigation

Peak plasma concentration (C_{max}) & time to peak concentration (t_{max}), directly found from the concentration vs. time data.

AUC0-t denotes area under curve from 0 to 24 hours, calculated using the linear trapezoidal technique, while AUC0-α signifies the area under the curve from zero hours-infinity.

AUC0-α got computed using formula AUC0-t + [Clast/K] (Clast: concentration in µg per ml at closing time point; K: elimination rate constant).

Multiple pharmacokinetic attributes, like AUC, elimination half-life (t½). Volume of distribution (V/f), total clearance (Cl/f), & mean residence time for all parameters calculated with the non-compartmental pharmacokinetic package RAMKIN, based following equations.

C_{max}

It is referred to as the concentration at which high concentration is observed.

t_{max}

Duration for drug to attain highest concentration in plasma is referred to as time of peak concentration.

t½

Duration necessary to decrease medication's concentration in the body by 50%. The elimination rate constant can be utilized to determine the elimination, presuming it follows a first-order course.

$t½ = 0.693/K$

Where K: elimination rate constant

AUC

It signifies bioavailability of medicine. Linear trapezoidal rule is applied from the initial hour to final sample time, t.

It represents region beneath zero moment curves.

For remaining area (Wagner's approximation)

$\therefore$ Total $AUC_{0-\alpha} = AUC_{0-t}+AUC_{t-\alpha}$

$= AUE_{0-t}+C_{(t)}/K$

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

Pharmacodynamic assessment

These were obtained from all groups on day 1, following which dosing continual until day 8, & blood samples got collected. Provide an estimation of the blood glucose levels.

Statistical Assessment

Statistical assessments were done through Glyburide and captopril in combination groups, as well as the concentration-response, were conducted using Student's paired T-Test, with P value of <0.05 deemed statistically substantial. Data got presented as Mean±SEM. Linear regressions got employed to ascertain connection among total plasma cholesterol & pharmacokinetic as well as pharmacodynamic characteristics.

RESULTS AND DISCUSSION

Table 1: Mean±SEM, plasma level (ng per ml) of Glyburide (single) & in Mixture with Captopril on 1st day in diabetic rat models

Time (hr)	Glyburide alone	Glyburide combination with Captopril
0	0±0	0±0
0.5	35.74±4.54	37.76±16.7
1	55.86±6.54	59.53±14.6
2	68.44 ± 8.32	71.36±15.3
4	87.35±5.26	92.35±13.8
6	62.63±4.97	81.65±14.7
8	44.56±5.32	53.65±7.43
24	0±0	0±0

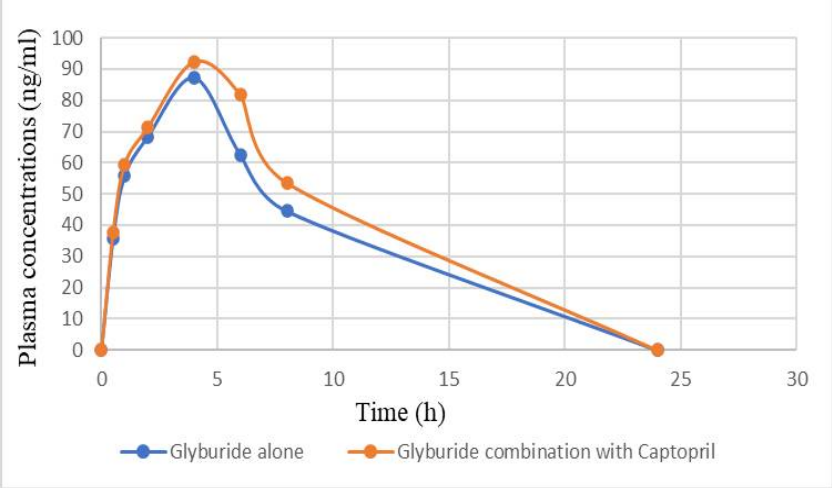

Figure 1: Plasma level (ng per ml) of Glyburide (single) & in Mixture of Captopril on day 1 in diabetic rat model

Table 2: Mean±SEM, plasma level (ng per ml) of Glyburide (single) & in mix with Captopril on 8th day in diabetic rats

Time (hr)	Glyburide alone	Glyburide combination with Captopril
0	45.75±4.63	43.32±5.65
0.5	64.35±8.35	67.65±3.26
1	75.65±8.76	78.26±6.54
2	82.65 ± 6.25	83.75±3.36
4	95.36±7.26	94.26±6.75
6	74.66±4.28	77.86± 5.26
8	53.86±4.41	65.27±3.24
24	25.38±6.35	31.36±9.76

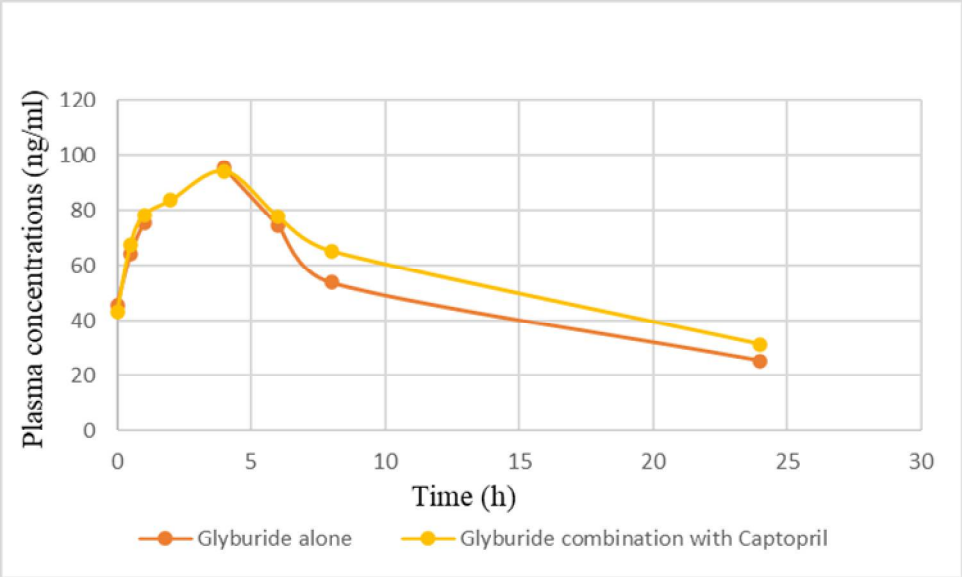

Figure 2: Plasma level (ng per ml) of Glyburide (single) % in mixture with Captopril on 8th day in diabetic rats

Table 3: Mean±SEM, Plasma level (ng/ml) of Captopril in healthy rat models and in diabetic rat models on 1st day in diabetic rat models

Time (hr)	Captopril in healthy Rat models	Captopril in Diabetic Rats
0	0±0	0±0
0.5	28.43±4.53	27.65±2.53
1	45.53±3.65	44.87±3.75
2	32.25±4.64	35.95±4.62
4	21.42±4.85	25.38±3.64
6	11.64±2.63	13.27±2.54
8	0±0	0±0
24	0±0	0±0

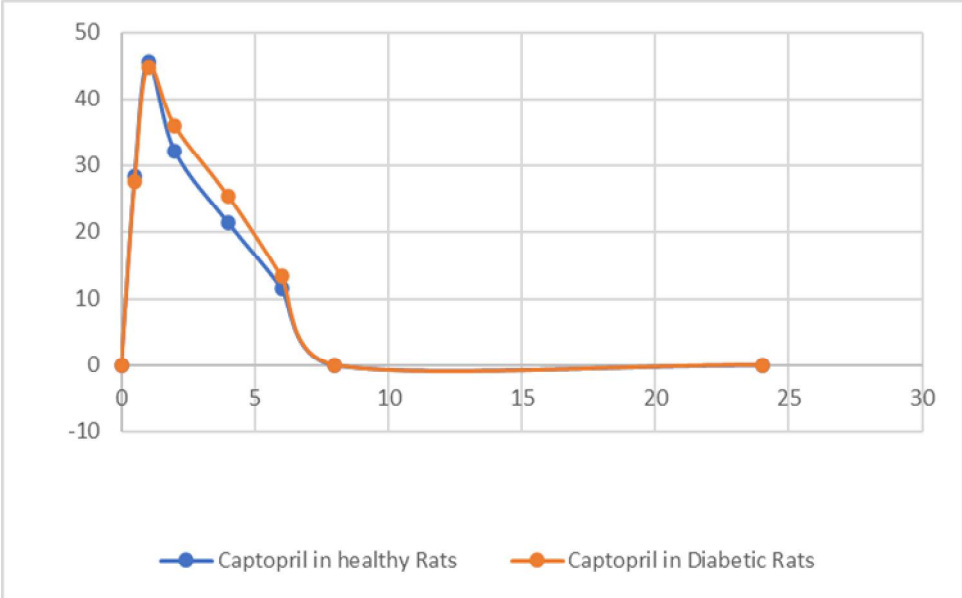

Figure 3: Plasma levels (ng per ml) of Captopril in healthy rat models and in diabetic rat models on 1st day in diabetic rats

Table 4: Mean±SEM, plasma level (ng per ml) of Captopril in healthy rat models and in diabetic rats on 8th day

Time (hr)	Captopril in healthy Rat models	Captopril in Diabetic Rats
0	5.65±1.32	7.85±1.43
0.5	31.65±4.53	33.63±2.74
1	49.37±3.65	53.83±3.92
2	36.86±4.64	38.52±4.27
4	25.38±4.85	27.83±3.53
6	19.64±2.63	17.26±2.36
8	15.96±2.53	12.72±2.53
24	8.64±2.62	9.38±2.52

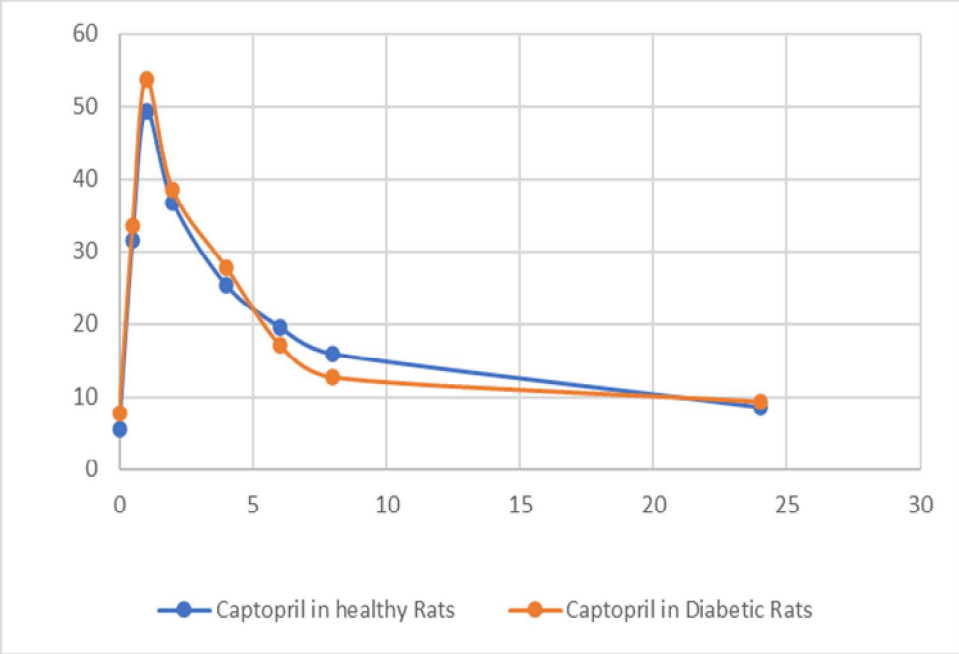

Figure 4: Plasma levels (ng per ml) of Captopril in healthy rat models and in diabetic rat models on 8th day in diabetic rat models

Table 5: Mean±SEM, plasma level (ng per ml) of Captopril (single) & in mixture with Glyburide on 1st day in diabetic rats

Time (hr)	Captopril alone	Captopril with Glyburide
0	0±0	0±0
0.5	27.65±2.53	35.32±3.38
1	44.87±3.75	49.38±5.86
2	35.95±4.62	41.27±6.58
4	25.38±3.64	32.75±5.39
6	13.27±2.54	21.53±4.41
8	0±0	0±0
24	0±0	0±0

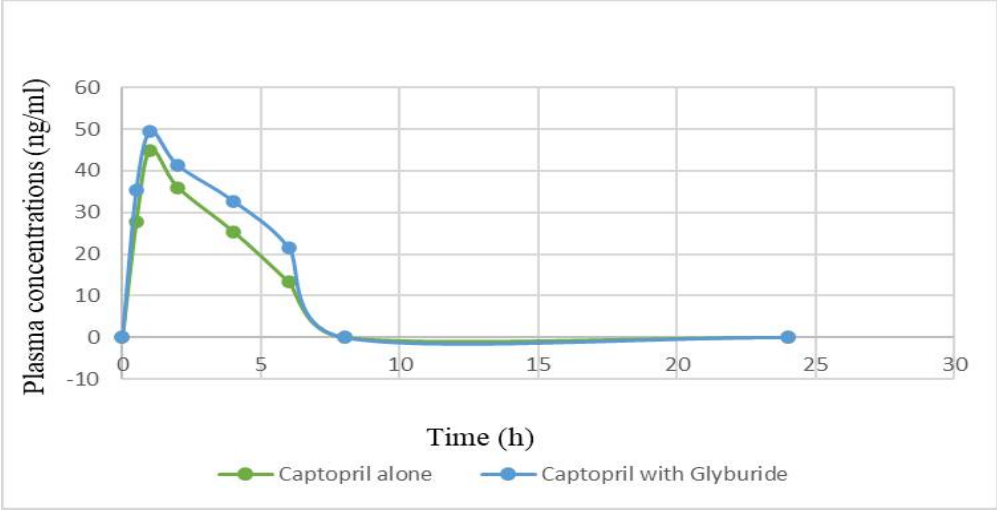

Figure 5: Plasma level (ng per ml) of Captopril (single) & in mixture of Glyburide on 1st day in diabetic rats

Table 6: Mean±SEM, plasma level of Captopril (single) & in mixture of Glyburide on 8th day in diabetic rat models

Time (hr)	Captopril alone	Captopril with Glyburide
0	7.85±1.43	12.44±2.43
0.5	33.63±2.74	37.96±4.75
1	53.83±3.92	55.37±6.47
2	38.52±4.27	38.36±2.38
4	27.83±3.53	31.74±6.66
6	17.26±2.36	21.86±2.26
8	12.72±2.53	13.25±4.52
24	9.38±2.52	9.53±2.25

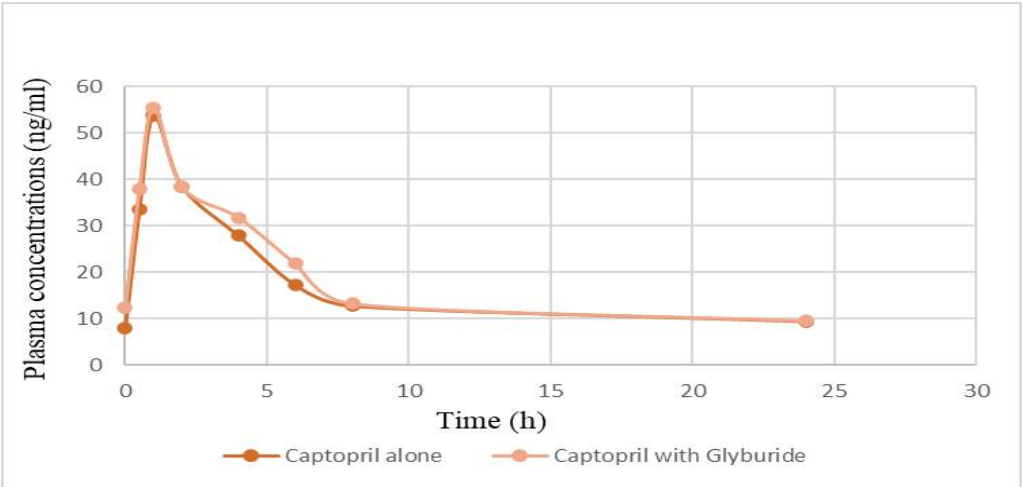

Figure 6: Plasma level (ng per ml) of Captopril (single) & in mixture by Glyburide on 8th day in diabetic rats

Plasma level (ng per ml) of Glyburide, both single & in mix with Captopril on 1st day, exhibited varying concentrations at diverse time intermissions: 0, 0.5, 1, 2, 4, 6, 8, & 24hours. The plasma concentrations of Glyburide alone on day 1 were 0±0, 35.74±4.54, 55.86±6.54, 68.44±8.32, 87.35±5.26, 62.63±4.97, 44.56±5.32, and 0±0, respectively. In contrast, the plasma concentrations of Glyburide in combination with Captopril were 0±0, 37.76±16.7, 59.53±14.6, 71.36±15.3, 92.35±13.8, 81.65±14.7, 53.65±7.43, and 0±0, respectively. The results are presented in Table1.

Plasma level (ng per ml) of Glyburide, both single & in mix with Captopril on 8th day, exhibited varying concentrations at diverse time intermissions: 0, 0.5, 1, 2, 4, 6, 8, & 24 hours. Plasma concentrations of

Glyburide alone were 45.75±4.63, 64.35±8.35, 75.65±8.76, 82.65±6.25, 95.36±7.26, 74.66±4.28, 53.86±4.41, and 25.38±6.35, respectively. In contrast, the concentrations of Glyburide in combination with Captopril were 43.32±5.65, 67.65±3.26, 78.26±6.54, 83.75±3.36, 94.26±6.75, 77.86±5.26, 65.27±3.24, and 31.36±9.76, respectively. The results are presented in Table 2.

Plasma levels (ng/ml) of Captopril both single & in mix with Glyburide on 1st day exhibited varying concentrations at different time intervals: 0, 0.5, 1, 2, 4, 6, 8, and 24 hours. The plasma concentrations of Captopril alone on day 1 were recorded as 0±0, 28.43±4.53, 45.53±3.65, 32.25±4.64, 21.42±4.85, 11.64±2.63, 0±0, and 0±0, respectively. In contrast, the plasma concentrations of Captopril in combination with Glyburide on day 1 were 0±0, 35.32±3.38, 49.38±5.86, 41.27±6.58, 32.75±5.39, 21.53±4.41, 0±0, and 0±0, respectively. The results were presented in Table 5.

Plasma level (ng per ml) of Captopril administered single 7 in mixture with Glyburide on 8th day exhibited varying amounts at different time intermissions: 0, 0.5, 1, 2, 4, 6, 8, & 24hours. The plasma concentrations of Captopril alone on day 8 were recorded as 7.85±1.43, 33.63±2.74, 53.83±3.92, 38.52±4.27, 27.83±3.53, 17.26±2.36, 12.72±2.53, and 9.38±2.52, respectively. In contrast, the plasma concentrations of Captopril in combination with Glyburide on day 8 were 12.44±2.43, 37.96±4.75, 55.37±6.47, 38.36±2.38, 31.74±6.66, 21.86±2.26, 13.25±4.52, and 9.53±2.25, respectively. The results are presented in Table 6.

Figure 1 illustrates plasma glyburide concentrations on day 1 at various time points, contrasting the administration of glyburide alone with combination conduct of glyburide & captopril on same day. Correspondingly, the plasma concentrations on day 8 are illustrated in Figure 2.

Figure 3 illustrates plasma captopril concentrations on day 1 in healthy rats at various time intervals, juxtaposed with the captopril combination treatment in diabetic rats on the same day. Correspondingly, the plasma concentrations on day 8 are illustrated in Figure 4.

Figure 5 illustrates plasma concentrations of captopril administered single on day 1 at dissimilar time intervals, in comparison to amalgamation treatment of captopril & glyburide on same day. Plasma concentrations on 8th day are illustrated in Figure 6.

The comparison of plasma concentrations of glyburide alone and in conjunction with captopril indicates that the plasma concentrations of captopril in the presence of glyburide exhibit no significant alterations.

Table 7: Mean±SEM, pharmacokinetic variables of Glyburide single & in mixture Captopril on 1st day

Variable	Glyburide	Glyburide+Captopril
C_{max} (ng/ml)	87.35±5.26	92.35±13.8
t_{max} (h)	4.00 ±0.46	4.00 ±0.31
AUC_{0-t} (ng/ml/h)	764.25 ±15.42	786.35 ±16.32
AUC_{0-inf} (ng/ml/h)	912.37 ±14.32	923.42 ±25.28
$T_{1/2}$ (h)	6.32 ±0.41	6.72 ±0.32

Table 8: Mean±SEM, Pharmacokinetic variables of Glyburide & Glyburide+Captopril on 8th day

Variables	Glyburide	Glyburide+Captopril
C_{max}(ng/ml)	95.36±7.26	94.26±6.75
t_{max} (h)	4.00 ±0.42	4.00 ±0.54
AUC_{0-t} (ng/ml/h)	897.36 ±15.24	942.26 ±21.44
AUC_{0-inf} (ng/ml/h)	923.25 ±23.43	1092.345 ±27.52
$T_{1/2}$ (h)	6.51 ±0.32	6.53 ±0.54

Table 9: Mean±SEM, pharmacokinetic variables of Captopril in healthy rat models & Captopril in diabetic rat models on 1st day

parameters	Captopril in healthy Rats	Captopril in Diabetic rats
C_{max}(ng/ml)	45.53±3.65	44.87±3.75
t_{max} (h)	1.00±0.43	1.0±0.53
AUC_{o-t} (n per /ml/h)	267.63±13.83	276.53±15.84
AUC_{0-inf} (ng/ml/h)	288.24±17.83	294.36±14.74
$T_{1/2}$ (h)	2.5±0.36	2.5±0.64

Table 10: Mean±SEM, pharmacokinetic variables of Captopril in healthy rat models & Captopril in diabetic rat models 8th day

Variables	Captopril in healthy Rats	Captopril in Diabetic rats
C_{max}(ng/ml)	49.37±3.65	53.83±3.92
t_{max} (h)	1.0±0.12	1.0±0.24
AUC_{0-t} (ng per ml/h)	326.36±35.74	337.26±24.84
AUC_{0-inf} (ng/ml/h)	359.74±24.85	371.92±31.42
$T_{1/2}$ (h)	2.5±0.42	2.5±0.26

Table 11: Mean±SEM, pharmacokinetic variables of Captopril and Captopril+Glyburide on 1st day

Variables	Captopril	Captopril+Glyburide
C_{max}(ng/ml)	44.87±3.75	49.38±5.86
t_{max} (h)	1.0±0.53	1.0±0.74
AUC_{0-t} (ng/ml/h)	276.53±15.84	298.35±13.42
AUC_{0-inf} (ng/ml/h)	294.36±14.74	314.43±15.42
$T_{1/2}$ (h)	2.5±0.64	2.5±0.54

Table 12: Mean±SEM, pharmacokinetic variables of Captopril and Captopril+Glyburide 8th day

Variables	Captopri	Captopril+Glyburide
C_{max}(ng/ml)	53.83±3.92	55.37±6.47
t_{max} (h)	1.0±0.24	1.0±0.63
AUC_{0-t} (ng per ml/h)	337.26±24.84	356.65±26.42
AUC_{0-inf} (ng/ml/h)	371.92±31.42	384.25±11.54
$T_{1/2}$ (h)	2.5±0.26	2.5±0.43

This study examined the pharmacokinetic properties of Glyburide and Captopril, both alone and in combination. Pharmacokinetic characteristics were analyzed. All results are presented in Table 7-12.
Pharmacokinetic parameters derived from the results indicate no significant difference in Glyburide's pharmacokinetics when administered alone or in combination with Captopril. Similarly, there was no significant variance observed in any pharmacokinetic variables of Captopril, whether administered single or in conjunction of Glyburide.

Table 13: Fasting serum Glucose concentration in normal & STZ-induced diabetic rat models on 1st day and 8th day

Treatment	Fasting serum Glucose concentration (mg/dl) restrained at steady intermissions	
	1st day	8th Day
Normal	68.33 ± 2.4	71.83 ± 2.81
Diabetic Control	449.6±16.64[a]	464.8 ±12.17[a]
Glyburide	81.46 ± 4.46[b]	65.53 ± 2.42 [b]
Glyburide with Captopril	75.76 ± 2.54[b]	68.54 ± 1.53 [b]

n=6; mean ±S.E.M
[a]P <0.001; [c]P <0.05 Vs Normal
[b]P <0.001 Vs Diabetic Control

DISCUSSION

Hypertension in diabetic patients constitutes a serious health issue, as the coexistence of both conditions is prevalent, linked to considerable morbidity & mortality, & regularly challenging for manage. Incidence of hypertension among diabetes patients is likely 1.5 to 2 times greater to that in the usual public [32]. Mitigating cardio vascular hazard is hence a paramount objective in treatment of diabetes. Microalbuminuria is a significant forecaster of cardiovascular events & is key elements of insulin resistance syndrome [33]. Various groups of antihypertensive medications can be employed to regulate blood pressure in diabetes. ATII type I receptor blockers (ARBs), CCB, thiazide diuretic, & ACE inhibitors

are prevalent. Cheung established that calcium channel blockers are frequently utilized in hypertensive individuals with diabetes mellitus [35].
Verapamil, a CCB, markedly diminished probability of diabetes onset [36]. Diabetics frequently utilize hypertension medications, often in conjunction with antidiabetic agents [37]. Administering ARBs to hypertensive and diabetic patients enhanced both macrovascular & microvascular changes [38]. Various categories of antihypertensive medications could be employed to regulate blood pressure in individuals with diabetes. CCBs, ATII receptor blocker type 1 (ARB), thiazide diuretic, & ACE inhibitors are prevalent. Cheung shown that calcium channel blockers are frequently utilized in hypertensive patients with diabetes. Comprehensive pharmacological management often include the treatment of Type II diabetes to achieve adequate glucose regulation & address coexisting medical problems. Drug interactions must be meticulously evaluated before administering antidiabetic medications [37]. Mitra [38] examined interactions of Diabecon (D-400), natural mineral antidiabetic medication. The primary aim of the study was to measure "in vitro" drug interactions of enalapril, captopril, & lisinopril having frequently used antidiabetic medications (glyburide, pioglitazone, glimepiride, & glibenclamide) by HPLC. Various groups of antihypertensive medications can be employed to regulate blood pressure in individuals with diabetes. These consist of CCBs, type 1 ARBs, thiazide diuretic, & ACE inhibitors. Cheung observed that calcium channel blockers are frequently utilized in hypertensive patients with diabetes. Standard pharmaceutical interventions typically encompass the managing of type II diabetes to attain adequate glucose regulation & the treatment of associated conditions. Drug interactions should be meticulously evaluated while administering antidiabetic medications. Mitra [39] did a study to observe interactions of Diabecon (D-400), a natural mineral antidiabetic medication. The primary aim of this study was to assess the "in vitro" drug interactions of enalapril, captopril, & lisinopril with frequently used antidiabetic medications (glyburide, pioglitazone, glimepiride, & glibenclamide) by HPLC. Study involved the analysis of pharmaceuticals by measurement of AUC. The data indicate that no substantial variation in availability or retention time was detected. Nonetheless, the data indicated that no interactions transpired, as HPLC revealed no substantial alterations in the availability of either drug.

CONCLUSION

This study indicates that single doses of glyburide, captopril, and captopril-treated diabetic rats, administered either separately or concurrently, had no statistically significant interactions in pharmacokinetic parameters. The pharmacodynamic interaction investigation indicated that the combination medication of glyburide and captopril resulted in substantial interactions. Moreover, we determined that the concurrent quantification of plasma levels of glyburide and captopril is feasible in the development of an HPLC approach. The concurrent administration of these two medications may offer advantages in diabetes management. Moreover, the combination therapy is safe and significantly advantageous for diabetes patients owing to its minimal pharmacokinetic interaction.

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