

Evaluation of Clarithromycin Effect on Hypoglycemia in the Experimental Rats

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ABSTRACT: The purpose of the present research was to evaluate of Clarithromycin effect on Hypoglycemia in the Experimental rats. There were clarithromycin interfere with cytochrome P-450 enzyme and thereby alter the pharmacokinetics of various drugs that are metabolized by this enzyme system when they are used concomitantly. Hence, there is the interactions between clarithromycin and sulfonylurea's (Glipizide & Gliclazide). Drug- drug interactions are one of the reasons for adverse drug events and should be predicted to avoid the possibility of drug resistance or ineffectiveness of the concomitantly administered drugs.

KEYWORDS: Clarithromycin, Hypoglycemia, Interactions, Glipizide, Gliclazide, Experimental Animals

I. INTRODUCTION

Drug- drug interactions are one of the reasons for adverse drug events and should be predicted to avoid the possibility of drug resistance or ineffectiveness of the concomitantly administered drugs. Potential drug interactions should be searched with particular effort in cases where drug combinations are conventionally prescribed. Drug interactions may be pharmacodynamic or pharmacokinetic type and much of the reported drug interactions are due to either CYP enzyme induction or inhibition. Generally pharmacokinetic interactions are more common than pharmacodynamic interactions.^{1,2}

During simultaneous treatment, there is an alteration in the efficacy of one or both the drugs. The inhibitors of drug metabolizing enzymes can significantly raise the plasma concentration of concomitantly administered drugs and the inducers can reduce the plasma concentration. The interaction may modify the diagnostic, preventive or therapeutic activity of either drug. Influence of one drug on the other are a preventable cause of

morbidity and mortality, yet their consequences in the community are not well characterized.³

Data from the literature indicates that the incidence of drug interaction ranges from 3 to 5% in patients taking a few drugs to 20% in patients receiving many drugs. It was estimated that the drug interactions up to 63% in hospitalized patients have been reported and even in USA, the drug interactions are reported to be fourth to sixth leading cause of death in hospitalized patients.⁴

Hence, while prescribing multidrug therapy there is need to undertake well characterized precautionary measures to minimize the problems of drug-drug interactions in multidrug therapy. Keeping the above statistics and reports in view, it is very much essential to understand the nature and possible mechanisms of drug interactions so as to accumulate the scientific data.

Diabetes mellitus is a metabolic disorder due to relative or absolute lack of insulin, resulting in elevated blood glucose levels in association with long term vascular and neurological complications.⁷

Once regarded as a single disease entity, diabetes mellitus is now seen as heterogeneous group of diseases characterized by a state of chronic hyperglycemia resulting from a diversity of etiologies, environmental and genetic factors acting jointly. Characteristically, diabetes is a long term disease with variable clinical manifestations and progression. Chronic hyperglycemia leads to number of complications – cardiovascular, renal, neurological and ocular others such as intercurrent infections. Currently the number of cases of diabetes worldwide is estimated to be around 150 million. This number is predicted to double by 2025, with the greatest number of cases being expected in China and India.⁸

Diabetes mellitus is the most common endocrine disorder characterized by persistent hyperglycemia with overall altered biochemistry

and resulting in many complications such as nephropathy, retinopathy, neuropathy, vascular disease, sexual impotence and low grade immunity leading to infections. It is estimated that 143 million people worldwide suffer from diabetes. Diabetes mellitus may be categorized in to two major types, type I accounting for 5% prevalence and type II for 95% prevalence among diabetics.

Despite the availability of many antidiabetic medicines in the market, diabetes and its related complications continue to be major medical problems. The currently used hypoglycemic drugs in the treatment of diabetes are not completely effective and are associated with adverse effects both in the short and long run.¹⁰

Cytochrome P-450 enzyme system plays a vital role in metabolism of sulfonylureas like Glipizide and Gliclazide. Hence, there exists a possibility of metabolism based drug-drug interactions, but very few of them have been reported. In the literature, it was indicated that, Glipizide is normally metabolized by microsomal enzyme system mainly by CYP3A4, CYP2C9, CYP2C199 and Gliclazide is metabolized by both CYP 2C9 and CYP 3A410. There are even reports that clarithromycin is an inhibitor of CYP 3A4.¹¹

In the literature it was indicated that macrolide antibiotics like erythromycin and clarithromycin enhanced the hypoglycemia induced by repaglinide. However, there are no reports of drug interactions between clarithromycin and sulfonylureas (Glipizide and Gliclazide) and hence, an attempt has been made to investigate the influence of clarithromycin on the hypoglycemic effects of sulfonylureas like Glipizide and Gliclazide in various animal models. Further, the study may be a great tool for the clinician to readjust the dose and frequency of administration of sulfonylureas when they are used concurrently with clarithromycin.^{12,13}

II. CALCULATION AND RESULTS

1. Influence of Clarithromycin on Blood Glucose Levels in Normal Albino Rats:

In the present study, the effect of clarithromycin (45 mg/kg) was assessed. It is evident from the table no. 1 that, treatment with clarithromycin (45 mg/kg) did not produce significant influence on the blood glucose levels in normal albino rats. The results are compiled in table no. 1 and graphically depicted in figure no. 1.

Time (h)	Blood glucose levels (mg%) with clarithromycin							Percentage blood glucose reduction with clarithromycin						
	1	2	3	4	5	6	Mean \pm SEM	1	2	3	4	5	6	Mean \pm SEM
0	95.36	103.42	110.32	92.38	85.63	91.51	96.43 \pm 3.65	-	-	-	-	-	-	-
1	97.5	110.31	102.61	98.32	84.3	93.58	94.97 \pm 3.25	-2.19	-6.89	6.98	-6.49	1.55	-2.26	-1.55 \pm 2.13
2	92.51	108.91	99.61	91.89	89.38	87.53	97.77 \pm 3.55	2.89	-5.3	9.7	0.53	-4.19	4.34	1.34 \pm 2.28
4	102.61	96.51	112.32	102.53	83.81	86.63	97.40 \pm 4.38	-7.6	6.68	-1.78	-10.98	2.17	5.33	-0.436 \pm 2.93
8	91.38	97.8	105.32	89.51	90.35	94.61	94.82 \pm 2.44	4.17	5.43	4.53	3.1	-5.51	3.38	3.22 \pm 1.37
12	90.36	107.51	108.51	87.61	93.51	99.36	97.81 \pm 3.60	5.24	-3.95	1.64	5.16	-9.2	8.57	12.61 \pm 2.67
18	105.31	92.51	106.31	91.35	88.91	84.39	94.79 \pm 3.66	-10.43	10.54	3.63	1.41	-3.68	9.83	-1.46 \pm 3.30
24	94.53	98.43	97.58	96.42	94.9	89.53	95.23 \pm 1.29	0.87	4.82	11.54	-4.14	9.76	7.95	1.88 \pm 3.22

Table No. 1: Blood glucose levels after the administration of clarithromycin (45 mg/kg) in normal albino rats.

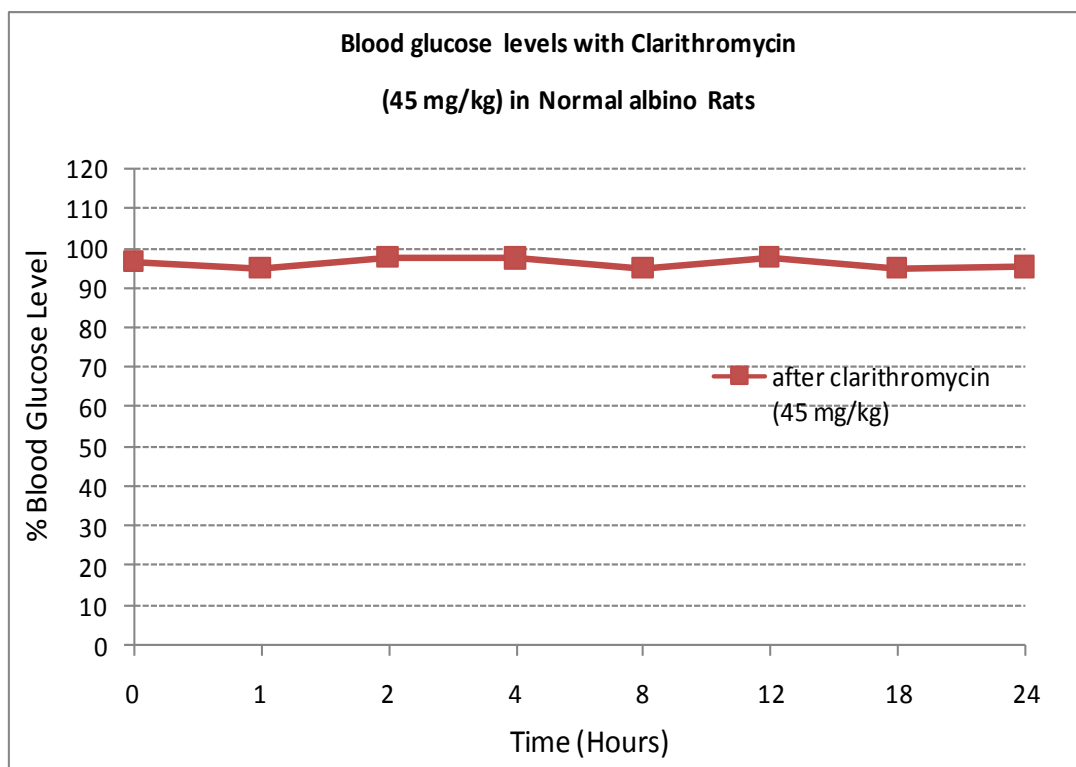


Figure No. 1: Blood glucose levels after the administration of clarithromycin (45 mg/kg) in normal albino rats.

2. Effect of Clarithromycin Pre-Treatment on Hypoglycemic Effect of Glipizide and Gliclazide on Normal Albino Rats:

Onset of hypoglycemia (time taken to reduce blood glucose level to the extent of 15%), duration of hypoglycemia (time duration in which a minimum of 15% reduction in blood glucose levels are maintained) and peak hypoglycemia (maximum blood glucose reduction) were the parameters considered for the evaluation of influence on Glipizide and Gliclazide induced hypoglycemia. Pretreatment with clarithromycin lower therapeutic dose (20 mg/kg twice a day) has not significantly altered the onset of hypoglycemia (1 h before and after treatment) and peak hypoglycemia was observed at 2nd h ($38.39 \pm 3.40\%$ before treatment and $42.46 \pm 2.94\%$ after treatment). But duration of hypoglycemia was altered from 17 h to 23 h in Glipizide induced hypoglycemia. The results of these findings are compiled in table no. 3 and graphically depicted in figure no. 2.

Pre-treatment with higher dose of clarithromycin (45 mg/kg twice a day for 7 days) has not altered the onset of hypoglycemia induced by Glipizide (i.e. 1 h before and 1 h after treatment), but peak hypoglycemia was altered

significantly i.e. ($38.97 \pm 0.92\%$ before treatment to $52.87 \pm 1.29\%$ after treatment) and the duration of hypoglycemia was shifted from 17 h before to 23 h after treatment in Glipizide induced hypoglycemia. These findings are recorded in table no. 5 and graphically show in figure no. 3.

Pretreatment with clarithromycin i.e. 20 mg/kg twice a day has not significantly altered the onset of hypoglycemia (1 h before treatment and 1 h after treatment) induced by Gliclazide. It was observed that peak hypoglycemia was seen in two different points ($44.62 \pm 1.96\%$ at 2nd h and $47.91 \pm 1.9\%$ reduction at 8th h before treatment and $47.34 \pm 2.20\%$ at 2nd h & $48.54 \pm 2.10\%$ at 8th h after treatment). However duration of hypoglycemia was not altered in Gliclazide induced hypoglycemia. The results are shown in table no. 7 and graphically shown in fig no.4.

The pre-treatment with higher therapeutic dose of clarithromycin (45 mg/kg twice a day for seven days) has not significantly altered the onset of hypoglycemia (i.e. from 1 h before to 1 h after treatment), but the peak hypoglycemia was altered significantly ($45.37 \pm 1.64\%$ & $46.00 \pm 1.23\%$ reduction before treatment to $55.35 \pm 1.66\%$ & $57.74 \pm 1.41\%$ reduction at 2nd and 8th h

respectively after treatment). However, duration of hypoglycemia was enhanced from 17 h before treatment to 23 h after treatment in Gliclazide

induced hypoglycemia. The results are compiled in table no. 9 and graphically shown in figure no. 5.

Time (h)	Percentage blood glucose reduction (mg%) with Glipizide							Percentage blood glucose reduction with Glipizide + clarithromycin						
	1	2	3	4	5	6	Mean \square SEM	1	2	3	4	5	6	Mean \square SEM
1	12.33	15.83	20.91	8.25	20.94	15.94	15.57 \square 1.95	16.35	17.71	12.46	17.71	27.56	19.82	18.60 \square 2.05
2	36.07	49.23	43.47	34.81	41.63	25.17	38.39 \square 3.40	47.76	40.3	49.19	45.81	39.69	32.02	42.46 \square 2.94
4	33.71	39.62	35.77	23.41	38.33	17.57	31.46 \square 3.62	41.5	27.09	38.42	36.58	37.69	26.2	34.58 \square 2.61
8	23.86	25.12	35.32	17.01	33.73	15.3	25.05 \square 3.37	32.04	28.83	27.73	31.53	31.14	23.17	29.07 \square 1.94
12	13.75	24.5	30.44	14.65	31.34	8.93	20.60 \square 3.85	23.23	32.05	31.89	27.59	27.82	15.93	26.41 \square 2.48
18	9.34	23.69	26.95	13.49	31.36	8.85	18.94 \square 3.93	21.11	31.17	3.81	26.64	23.06	13.46	24.37 \square 2.73
24	6.05	23.58	17.45	4.61	13.5	4.99	11.69 \square 3.18	14.13	25.94	20.24	18.33	17.26	12.71	18.10 \square 1.92

Table No. 3: Percentage blood glucose reduction with Glipizide (200 μg /kg) in normal albino rats before and after clarithromycin (20 mg/kg twice a day) treatment.

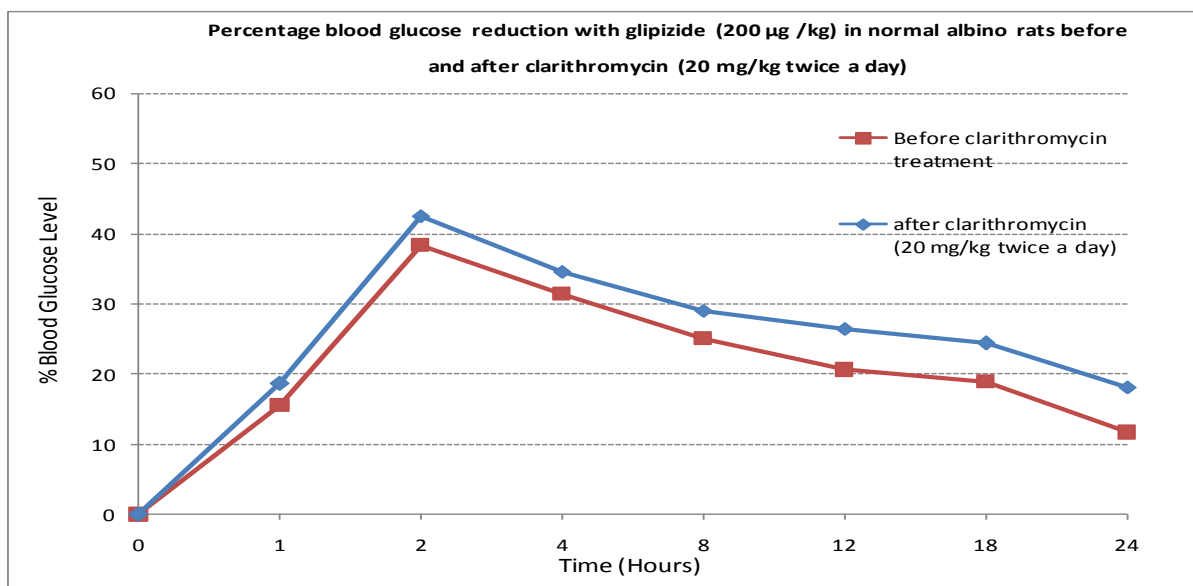


Figure No. 2: Percentage blood glucose reduction with Glipizide (200 μg /kg) in normal albino rats before and after clarithromycin (20 mg/kg twice a day) treatment.

Table No. 5 Percentage blood glucose reduction with Glipizide (200µg/kg) in normal albino rats before and after clarithromycin (45 mg/kg twice a day) treatment.

Time (h)	Percentage blood glucose reduction (mg%) with Glipizide							Percentage blood glucose reduction with Glipizide + clarithromycin						
	1	2	3	4	5	6	Mean SEM	1	2	3	4	5	6	Mean SEM
1	21.48	16.59	24.45	23.8	14.86	20.85	20.33±1.57	8.67	15.71	14.97	22.88	20.1	16.53	16.47±1.98
2	42.39	41.33	37.6	37.8	37.62	37.08	38.97±0.92	53.65	54.6	51.02	47.65	53.47	56.79	52.87±1.29
4	32.43	32.22	27.57	31.26	30.57	36.1	31.68±1.13	42.57	44.92	45.23	41.51	43.15	43.81	43.52±0.58
8	27.44	37.15	19.21	30.85	30.02	31.7	29.39±2.41	32.42	38.23	56.56	31.76	26.96	40.45	34.39±2.01
12	18.37	31.38	22.21	25.7	21.37	25.61	24.10±1.84	25.9	35.26	35.49	25.96	21.72	27.92	28.70±2.26
18	16.06	27.71	19.39	21.72	8.97	20.89	19.12±2.55	17.49	33.83	21.98	25.95	15.98	20.11	22.55±2.67
24	9.3	16.59	10.69	16.01	11.41	8.32	12.05±1.41	14.96	26.34	24.62	25.43	15.76	19.98	21.18±2.05

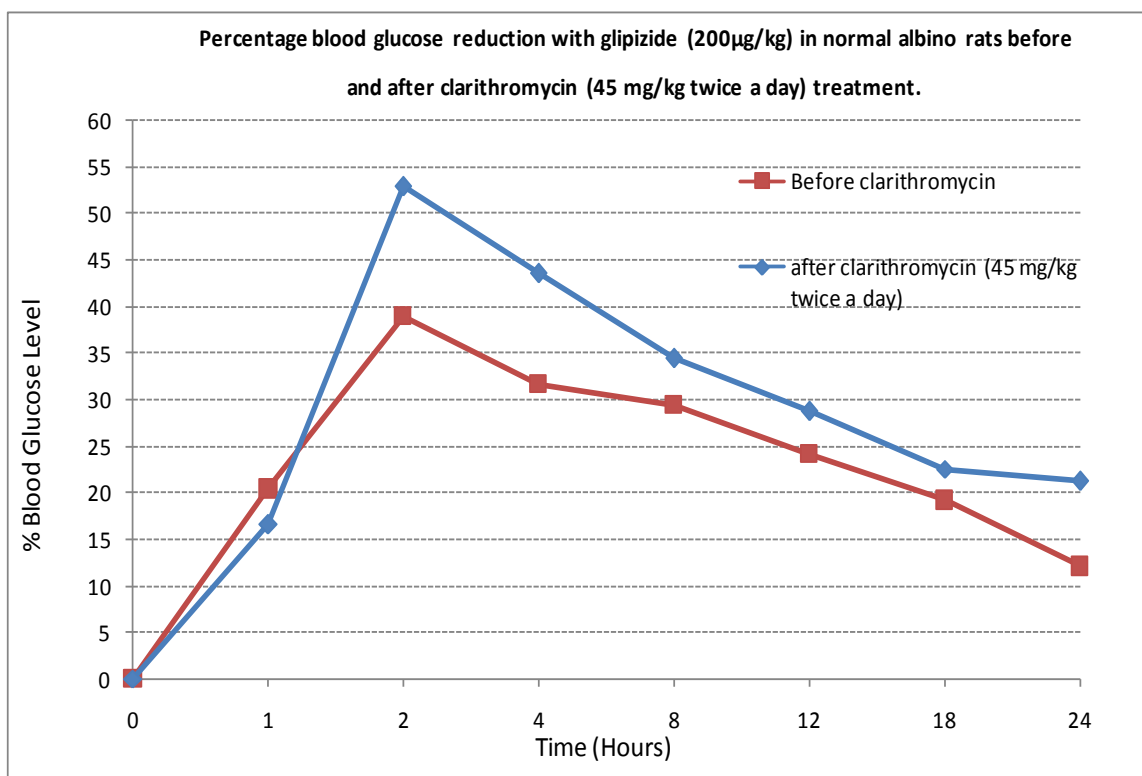


Figure No. 3 Percentage blood glucose reduction with Glipizide (200µg/kg) in normal albino rats before and after clarithromycin (45 mg/kg twice a day) treatment.

Time (h)	Percentage blood glucose reduction (mg%) with Gliclazide							Percentage blood glucose reduction with Gliclazide + clarithromycin						
	1	2	3	4	5	6	Mean \pm SEM	1	2	3	4	5	6	Mean \pm SEM
1	19.64	22.61	21.63	22.42	25.35	24.49	22.71 \pm 0.84	22.51	24.38	20.37	18.51	23.51	27.33	23.32 \pm 1.31
2	40.11	39.07	52.37	46.16	43.99	46.03	44.62 \pm 1.96	43.17	41.95	40.33	46.05	47.02	48.65	47.34 \pm 2.20
4	32.61	26.12	44.44	52.47	39.37	36.23	35.20 \pm 2.50	37.01	35.76	35.14	39.85	38.28	41.56	39.79 \pm 1.54
8	44.34	41.79	54.68	46.43	50.52	49.74	47.91 \pm 1.9	46.95	45.39	47.17	52.3	53.25	53.03	48.54 \pm 2.1
12	29	21.84	41.36	33.51	44.04	24.33	32.34 \pm 2.6	30	20.89	29.38	21.24	33.92	36	28.57 \pm 5.4
18	19.63	19.21	23.16	28.87	14.91	15.04	20.13 \pm 2.1	27.8	16.65	26.43	17.94	21.8	20.74	21.89 \pm 1.85
24	8.83	4.49	13.92	4.15	13.06	2.24	7.78 \pm 2.0	10.6	12.88	17.85	12.44	14.64	6.92	12.55 \pm 1.50

Table No. 7: Percentage blood glucose reduction with Gliclazide (2.8mg/kg) in normal albino rats before and after clarithromycin (20mg/kg twice a day) treatment.

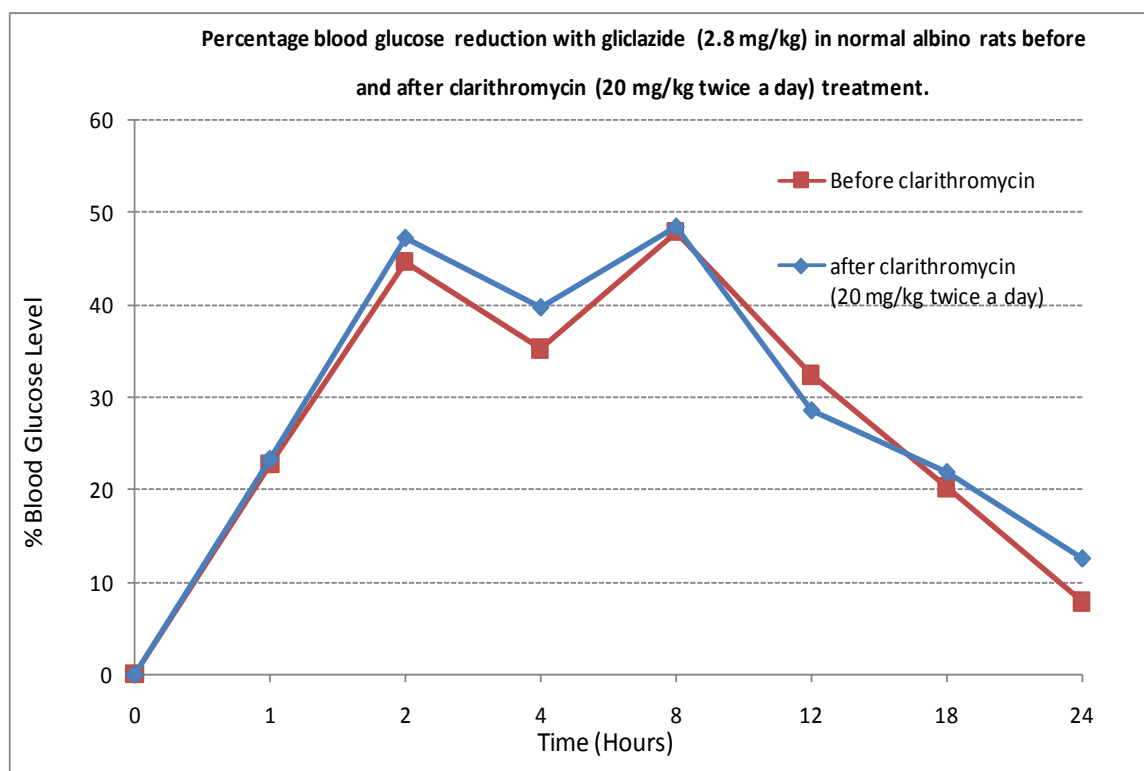


Figure No. 4: Percentage blood glucose reduction with Gliclazide (2.8mg/kg) in normal albino rats before and after clarithromycin (20mg/kg twice a day) treatment.

Table No. 9: Percentage blood glucose reduction with Gliclazide (2.8mg/kg) in normal albino rats before and after clarithromycin (45mg/kg twice a day) treatment.

Time (h)	Percentage blood glucose reduction (mg%) with Gliclazide							Percentage blood glucose reduction with Gliclazide + clarithromycin						
	1	2	3	4	5	6	Mean \pm SEM	1	2	3	4	5	6	Mean \pm SEM
1	22.48	51.39	28.83	25.39	21.82	17.89	24.63 \pm 2.01	28.15	32.81	33.94	27.32	29.37	25.01	29.43 \pm 1.38
2	42.84	44.23	46.56	39.44	50.21	48.96	45.37 \pm 1.64	55.59	59.05	56.11	47.44	57.56	56.44	55.35 \pm 1.66
4	36.6	42.8	38.33	38.42	41.28	27.33	37.46 \pm 2.22	48.76	49.21	52.45	43.49	51.66	51.89	49.57 \pm 1.36
8	46.82	46.43	47.41	41.12	50.41	44.84	46.00 \pm 1.23	58.75	59.87	57.31	51.79	62.01	56.74	57.74 \pm 1.41
12	19.54	23.68	21.6	29.48	24.38	28.56	24.54 \pm 1.58	40.07	34.07	40.78	25.14	37.08	34.18	35.22 \pm 2.32
18	12.5	14.21	16.43	10.4	16.43	16.9	14.28 \pm 0.99	19.17	19.56	26.63	17.31	15.31	16.85	19.13 \pm 1.62
24	6.28	7.34	5.82	4.32	7.6	0.37	5.28 \pm 1.09	14.77	17.81	20.12	16.78	9.69	12.75	15.32 \pm 1.52

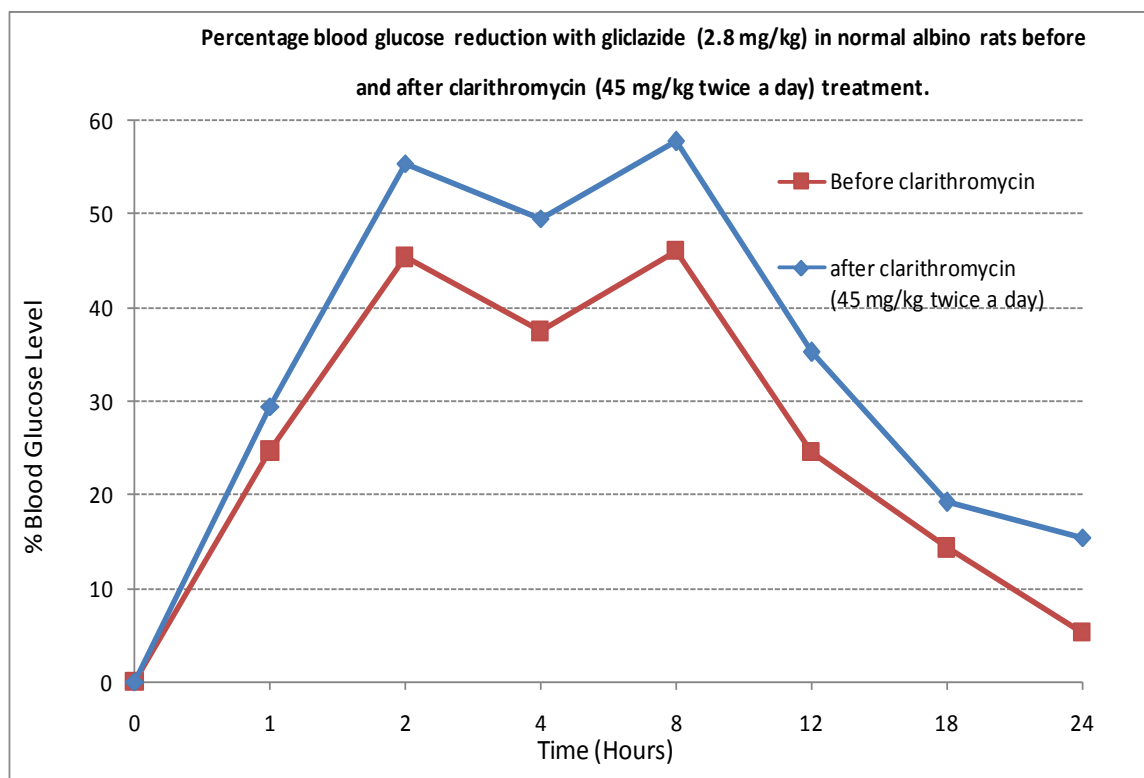


Figure No. 5: Percentage blood glucose reduction with Gliclazide (2.8mg/kg) in normal albino rats before and after clarithromycin (45mg/kg twice a day) treatment.

3. Effect of Clarithromycin Pre-Treatment on Anti Diabetic Activity of Glipizide and Gliclazide in Diabetic Rats:

Earlier studies in this project revealed that clarithromycin (45 mg/kg twice a day for 7 days) pre-treatment has altered the hypoglycemic effect of sulfonylureas (like Glipizide and Gliclazide). However, clarithromycin pre-treatment for 7 days has slightly altered the parameters of hypoglycemia induced by sulfonylureas such as Glipizide and Gliclazide in both carnivorous and herbivorous species. Therefore in the next part of our study, the diabetic rats (alloxan induced) were used to verify the obtained results in pathophysiological conditions such as diabetes mellitus in rats. Pretreatment with clarithromycin (45 mg/kg twice a day for seven days) has not significantly altered the onset of hypoglycemia (i.e. from 1 hrs before

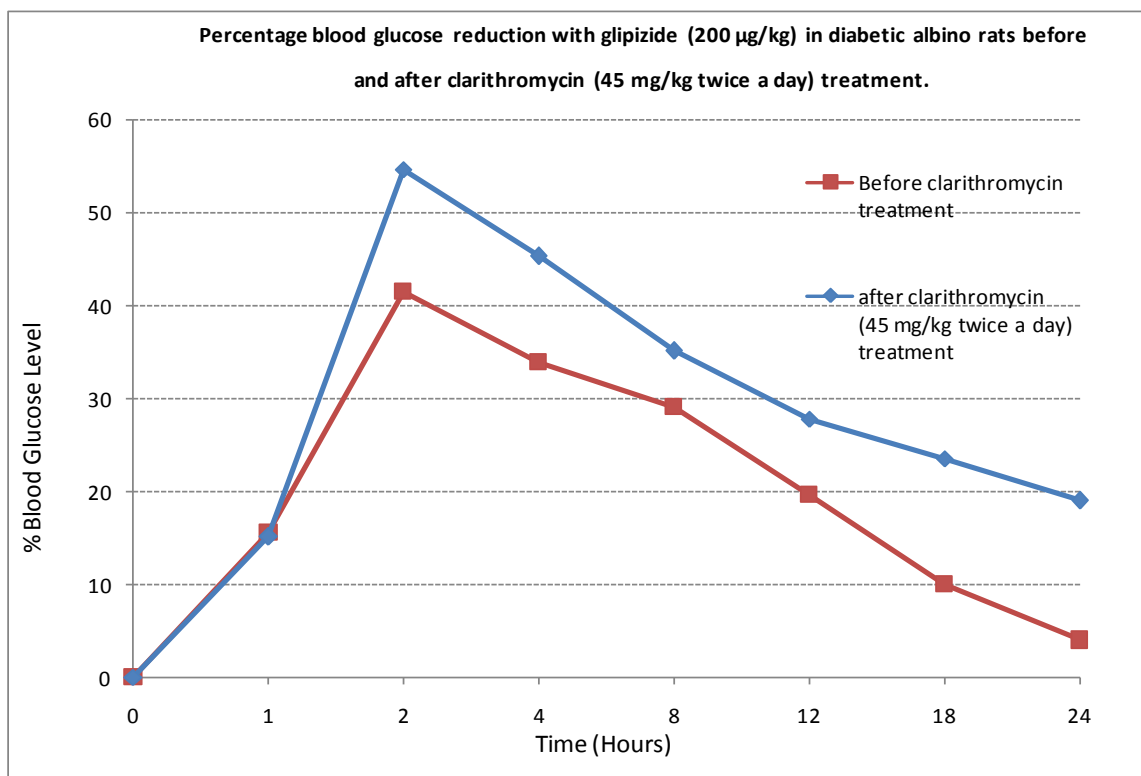
treatment to 1 hrs after treatment), but peak hypoglycemia (i.e from 41.46 ± 1.71 % reduction to 54.70 ± 1.18 % reduction) and duration of hypoglycemia was enhanced from 11 h to 23 h induced by Glipizide. The results are depicted in table no. 11 and graphically shown in figure no. 6.

Pre-treatment with clarithromycin (45 mg/kg twice a day for seven days) did not significantly altered the onset of hypoglycemia, but peak hypoglycemia (i.e. from 45.60 ± 1.19 % & 41.58 ± 1.58 % reduction before to 54.27 ± 1.46 % & 45.39 ± 1.08 % reduction after treatment at 2nd and 8th h respectively) and enhanced the duration of hypoglycemia from 17 h to 23 h) induced by Gliclazide.

The results are shown in table no. 13 and graphically shown in figure no. 7.

Time (h)	Percentage blood glucose reduction with Glipizide							Percentage blood glucose reduction with Glipizide + clarithromycin						
	1	2	3	4	5	6	Mean \pm SEM	1	2	3	4	5	6	Mean \pm SEM
1	12.09	14.65	18.51	19.55	14.52	14.61	15.65 \pm 1.14	9.88	18.84	17.62	19.75	12.55	12.26	15.15 \pm 1.67
2	41.01	34.12	41.83	41.31	43.62	46.9	41.46 \pm 1.71	54.72	56.4	57.74	56.63	49.97	52.69	54.70 \pm 1.18
4	36.06	23.75	38.36	38.2	32.26	35.6	33.98 \pm 2.25	51.12	46.19	47.65	45.98	41.14	39.76	45.30 \pm 1.71
8	31.96	25.87	35.4	32.31	21.16	28.27	29.16 \pm 2.10	37.68	39	46.6	36.05	28.77	22.57	35.11 \pm 3.42
12	19.73	19.01	25.82	19.44	17.11	16.7	19.63 \pm 1.33	27.78	26.21	39.68	29.86	23.35	20.18	27.84 \pm 2.74
18	10.73	12.54	13.84	6.7	10.73	5.58	10.02 \pm 1.32	23.89	22.93	33.9	22.31	20.57	17.62	23.53 \pm 2.26
24	5.69	6.19	5.93	2.14	1.01	3.39	4.05 \pm 0.89	18.48	22.44	25.95	19.25	12.8	13.28	19.04 \pm 1.93

Table No. 11 Percentage blood glucose reduction with Glipizide (200 μ g/kg) in diabetic albino rats before and after clarithromycin (45 mg/kg twice a day) treatment.



Fig

re No. 6: Percentage blood glucose reduction with Glipizide (200 µg/kg) in diabetic albino rats before and after clarithromycin (45 mg/kg twice a day) treatment.

Time (h)	Percentage blood glucose reduction with Gliclazide							Percentage blood glucose reduction with Gliclazide + clarithromycin						
	1	2	3	4	5	6	Mean ± SEM	1	2	3	4	5	6	Mean ± SEM
1	16.34	22.9	20.39	17.45	22.56	22.59	20.37 ± 1.16	15.34	18.01	15.35	21.77	19.71	13.42	17.26 ± 1.12
2	46.91	45.22	49.9	45.63	40.9	45.06	45.60 ± 1.19	53.45	59.33	50.25	54.32	50.86	57.41	54.27 ± 1.46
4	28.2	38.66	35	35.3	29.82	29.61	32.79 ± 1.69	39.83	42.89	33.83	41.23	32.34	44.4	39.08 ± 2.00
8	45.47	44.59	38.34	36.15	39.87	44.81	41.58 ± 1.58	44.1	47.29	49.11	45.99	41.62	44.26	45.39 ± 1.08
12	22.26	35.07	31.34	29.79	17.81	27.47	27.29 ± 2.57	43.36	46.47	31.85	41.92	31.66	38.09	38.89 ± 2.51
18	18.86	25.27	21.46	21.28	15.35	13.71	19.32 ± 1.74	27.07	28.23	16.46	31.74	20.39	17.44	23.55 ± 2.57
24	6.48	10.84	4.3	3.3	3.32	6.03	5.71 ± 1.16	23.37	18.63	12.73	27.19	13.42	19.08	18.79 ± 2.30

Table No.13 : Percentage blood glucose reduction with Gliclazide (2.8 mg/kg) in diabetic albino rats before and after clarithromycin (45 mg/kg twice a day) treatment.

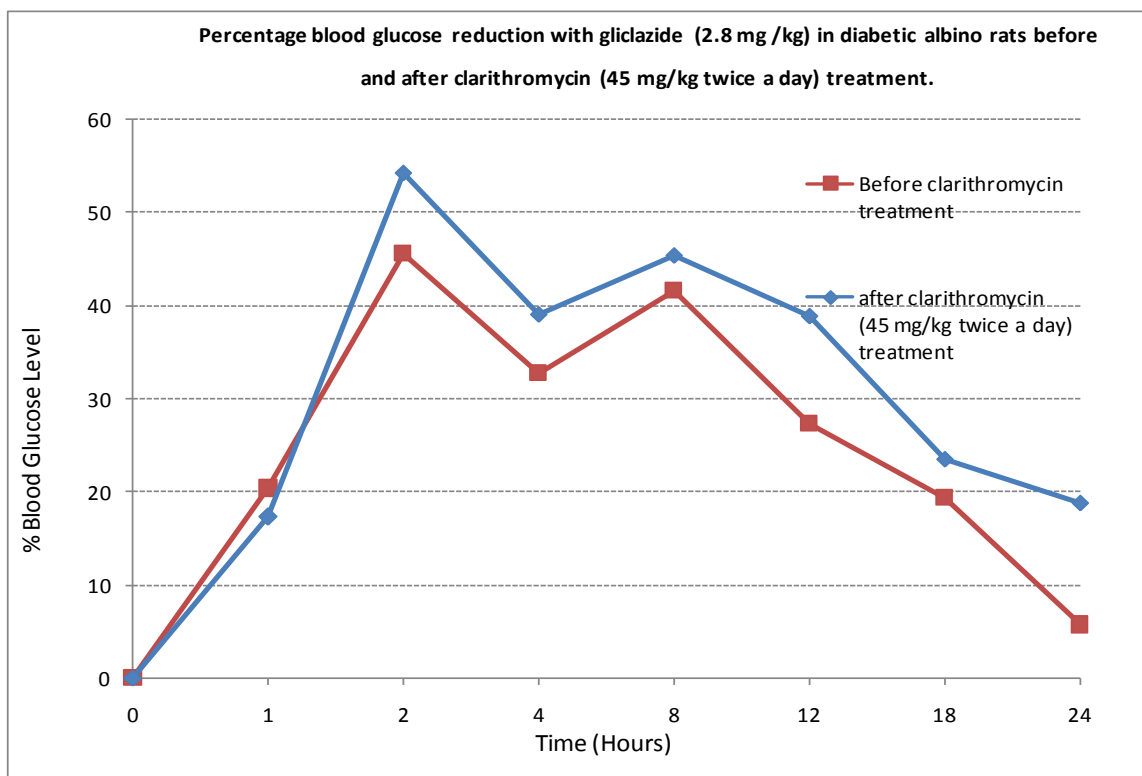


Figure No.7 : Percentage blood glucose reduction with Gliclazide (2.8 mg/kg) in diabetic albino rats before and after clarithromycin (45 mg/kg twice a day) treatment.

III. RESULTS SUMMARIZED

The results of our study are summarized and compiled in the table's no. 14 to 16. The conclusions drawn out of these discussions are recorded in the following pages.

Sl. No.	Treatment	Dose	Onset of action(h)	More than 15% reduction in blood glucose maintained for (h)	Duration of action (h)	Peak effect seen at time 't' (h)	Maximum blood glucose reduction %	Inference
1	Clarithromycin	45 mg/kg	-	□	□	□		Clarithromycin has not shown any hypoglycemic effect.
2	Glipizide (Group I)	200 □g/kg	1	17h	17h	2	38.39 □3.40	Onset of action and peak effect is not altered but duration of hypoglycemia was enhanced.
3	Clarithromycin + Glipizide (Group I)	20 mg/kg/ twice a day for 7 days + 200 □g/kg	1	23 h	23h	2	42.46 □2.94	
4	Glipizide (Group II)	200 □g/kg	1	17h	17 h	2	38.97 □ 0.92	
5	Clarithromycin + Glipizide (Group II)	45 mg/kg/ twice a day for 7 days + 200 □g/kg	1	23h	23h	2	52.87 □ 1.29	Onset of action was not altered but duration of hypoglycaemia and peak effect were enhanced

Table No. 14: Effect of clarithromycin treatment on hypoglycemic activity of Glipizide in normal albino rats.

Onset of action: Time taken to reduce minimum of 15% reduction in blood glucose levels.

Duration of action: Time duration in which a minimum of 15% reduction in blood glucose levels are maintained

Table No. 15: Effect of clarithromycin treatment on hypoglycemic activity of Gliclazide in normal albino rats.

Sl. No.	Treatment	Dose	Onset of action(h)	More than 15% reduction in blood glucose maintained for (h)	Duration of action (h)	Peak effect seen at time 't' (h)	Maximum % blood glucose reduction	Inference
1	Clarithromycin	45 mg/kg	□	□	□	□	□	Clarithromycin has not shown any hypoglycemic effect
2	Gliclazide (Group I)	2.8 mg/kg	1h	17h	17h	2 h & 8 h	44.62 □ 1.96	Onset of action, peak effect and duration of hypoglycemia were not altered significantly.
3	Clarithromycin + Gliclazide (Group I)	20 mg/kg/day for 7 days + 2.8 mg/kg	1h	17h	17h	2 h & 8 h	47.91 □ 1.9	
							47.34 □ 2.20 48.54 □ 2.1	
4	Gliclazide (Group II)	2.8 mg/kg	1h	17h	17h	2 h & 8 h	45.37 □ 1.64	Onset of action not altered significantly; But duration of hypoglycemia and peak effect were enhanced.
5	Clarithromycin + Gliclazide (Group II)	45 mg/kg/day for 7 days + 2.8 mg/kg	1h	23h	23h	2 h & 8 h	46.00 □ 1.23 55.35 □ 1.66 57.74 □ 1.41	

Onset of action: Time taken to reduce minimum of 15% reduction in blood glucose levels.

Duration of action: Time duration in which a minimum of 15% reduction in blood glucose levels are maintained.

Table No. 16: Effect of clarithromycin treatment on hypoglycemic activity of Glipizide and Gliclazide in diabetic rats.

Sl. No.	Treatment	Dose	Onset of action(h)	More than 15% reduction in blood glucose maintained for (h)	Duration of action (h)	Peak effect seen at time 't' (h)	Maximum % blood glucose reduction	Inference

1	Clarithromycin	45 mg/kg	□	□	□	□	□	Clarithromycin has not shown any hypoglycemic effect
2	Glipizide (Group I)	200 µg/kg	1h	11h	11h	2 h	41.46 ± 1.71	Onset of action and duration of hypoglycemia was enhanced. But peak effect not altered.
3	Clarithromycin + Glipizide (Group I)	45 mg/kg/twice a day + for 7 days + 200 µg/kg	1h	23h	23h	2 h	54.70 ± 1.18	
4	Gliclazide (Group II)	2.8 mg/kg	1h	17h	17h	2 h & 8h	45.60 ± 1.19 & 41.58 ± 1.58	Onset of action and peak effect were not altered but duration of hypoglycemia was enhanced.
5	Clarithromycin + Gliclazide (Group II)	45 mg/kg/twice a day for 7 days + 2.8 mg/kg	1h	23h	23h	2 h & 8h	54.27 ± 1.46 & 45.39±1.08	

Onset of action: Time taken to reduce minimum of 15% reduction in blood glucose levels.

Duration of action: Time duration in which a minimum of 15% reduction in blood glucose levels are maintained.

IV. CONCLUSION

- The higher therapeutic dose of clarithromycin significantly influenced the hypoglycemia induced by Glipizide and Gliclazide in all the studied animals and hence it can be concluded that clarithromycin inhibits the enzyme responsible for the metabolism of studied sulfonylureas.
- It may be further concluded that, during simultaneous treatment with clarithromycin and sulfonylureas, the dose and frequency of administration of the latter may be required.

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