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Pharmacokinetic Drug-drug interaction of Amiodarone with Nateglinide and Pioglitazone in different animal models

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ABSTRACT

There are certain diseases for which chronic treatment is needed. If two or more diseases are present in a single patient, the drugs for both the diseases are used concomitantly for a chronic period. Therefore there is every possibility that drug-drug interaction may develop and may pose problems of either overdoses or ineffectiveness of given dose. So it is very much essential to evaluate the drug-drug interaction in those conditions. Especially in the case of diabetes mellitus regulation of blood glucose level is highly essential and important. But when a drug potentiates the effect of antidiabetic agent, the severe hypoglycemia may be developed or if it inactivates the antidiabetic agents then the doses may be ineffective. Normally in those patients the antidiabetic agents e.g. pioglitazone and nateglinide etc. are administered along with anti-arrhythmic agent like amiodarone, lidocaine, procainamide, propranolol, digitalis etc. are given. The given study is carried out to understand drug interaction between the selected antiarrhythmic drugs with anti diabetic drugs on the pharmacokinetics of anti diabetic drugs. By Blood glucose measurement the pharmacokinetic response were determined. Our studies in rats suggested that dug-drug interaction occurs between amiodarone and oral antidiabetic agents like pioglitazone and nateglinide when they are used concomitantly in healthy conditions. However the interaction in the pathophysiological conditions like in diabetes was not clear. Hence, in the fourth phase of our study the diabetic rats (Alloxan induced diabetic rats) were used, pioglitazone and nateglinide were given to diabetic animals and the onset of hypoglycemia, duration of hypoglycemia and peak antidiabetic effect was determined. The results in diabetic animals are indicating that drug-drug interaction occur even in pathophysiological conditions. It was observed in all two types of animals i.e. healthy rats and diabetic rats that, drug-drug interaction occur, when amiodarone, pioglitazone and nateglinide are administered concomitantly. Since the amiodarone has shown significant effect on onset of hypoglycemia, it may be inferred that amiodarone interferes with absorption of oral antidiabetic agents. However amiodarone have significantly enhanced the hypoglycemia in both induced by pioglitazone and nateglinide. This may be due to fact that amiodarone mainly inhibit CYP2C9 and CYP3A423, which is involved in the metabolism of pioglitazone and nateglinide.

Keywords:*Amiodarone, Pioglitazone, Nateglinide, drug-drug interaction, hypoglycemia, Alloxan*

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INTRODUCTION

Drug interactions can have desired, reduced or unwanted effects. The probability of interactions increases with the number of drugs taken. The high rate of prescribed drugs in elderly patients (65-year-old patients take an average of 5 drugs) increases the likelihood of drug interactions and thus the risk that drugs themselves can be the cause of hospitalization. [1] Patients with type 2 diabetes mellitus (T2DM) often do not suffer solely from symptoms of increased blood glucose levels. In the majority of cases, several comorbidities are present with the need of additional pharmacological treatment. Concomitant diseases such as hypertension and high blood lipids can lead to both microvascular and macrovascular complications. [2] Diabetes mellitus is one such disorder, which requires vigilant management of its therapy with respect to blood glucose levels, since both hyperglycemia and hypoglycemia are undesirable. In such a situation, there may be chances for interactions between antidiabetic and antiarrhythmic drugs, which may be beneficial or harmful. Consequently, there is a need to monitor drug therapy in polypharmacy in order to gain a better therapeutic effect with a lower rate of risk.[3] Drug interactions are often categorized as pharmacodynamics or pharmacokinetic in nature. [4]

Amiodarone and oral hypoglycaemic agents like pioglitazone and nateglinide are widely accepted drugs in the treatment of cardiac arrhythmia and type II diabetes respectively.[5] Amiodarone is one such anti-arrhythmic agent which is inhibitor of CYP2D6, CYP1A2, CYP3A4, CYP3A5, CYP3A7 and CYP2C9 enzyme

system.[6] Here anti-diabetic drugs like Nateglinide and Pioglitazone metabolised by CYP3A4 and CYP2C9.[7,8] As these drugs share a common enzyme system of their metabolism, there may exist drug-drug interaction between these drugs on concomitant administration. However its interaction with pioglitazone and nateglinide is not reported. Hence, the present study is planned to understand the possible drug-drug interaction between hypoglycaemic agents like pioglitazone and nateglinide and anti-arrhythmic drug like amiodarone in healthy rats and diabetic rats. The main parameters that are considered to study the interaction between the above mentioned drugs are the influence of amiodarone on the onset, duration and peak hypoglycemia produced by pioglitazone and nateglinide, when they are used simultaneously. Therefore the study is to assess the possibility of potential interaction of pioglitazone and nateglinide with amiodarone is very much needed.

MATERIALS AND METHODS

Animals:

All healthy adult swiss albino wistar rats of either sex weighing between or 160 to 180 gm were used for the study. A total of 50 rats(either sex)were selected for the current study.

Induction of diabetes:[3]

Induction of diabetes Albino rats of either sex were used for the induction of diabetes. These animals were injected with a freshly prepared aqueous solution of alloxan monohydrate in two doses of 100 mg/kg and 50 mg/kg body weight intraperitoneally for two consecutive days. Then 10% dextrose was administered to combat the immediate hypoglycemia. Blood sugar was measured and rats showing fasting blood sugar levels above 250 mg/dL were selected for the study.

Method for oral administration:[9]

Oral feeding administration was done by oral feeding needle.

Method for blood sampling: [10, 11, 12]

The rat was anesthetized by anaesthetic ether in anaesthetic chamber. After small anesthetized rat was taken up from anaesthetic chamber. Now put animal on operation table and tail is squeezed with ethanol to dilate the vein and cut the tip of tail and blood is collected in the epindroff tubes containing pinch of anticoagulant mixture (sodium fluoride and potassium oxalate in 1:3 ratio).

Method for collection of plasma: [10, 11]

The plasma was obtained by centrifuging the blood samples at 3000 rpm for 15min; decanting the supernatant fluid into the clean and dry test tubes.

Estimation of blood glucose

Enzyme, GOD-POD endpoint colorimetry[13]

The GOD/POD method was adopted in the present study. [14].

Experimental procedure:

Phase I :

Group of six albino rats of either sex weighing between 160-180 gm were selected for the study. The animals were randomly distributed into 4 groups (n=6, I, II, III, IV, v); each group was consisting of 6 animals.

On the previous day of experimentation, the food was withdrawn 18-hrs in advance. However water was allowed *ad libitum*. The fasting was continued till the completion of the experiment. On next day, the blood samples were withdrawn from tail vein (0.5 ml, each) for determination of basal glucose concentration.

Thereafter, the animals of first group were administrated with suspension of Amiodarone 50 mg/kg trough oral route.

Phase II:

Animals of second group were administrated with suspension of pioglitazone 0.3 mg/kg trough oral route.

Animals of third group were administrated with suspension of nateglinide 50mg/kg through oral route.

Phase III:

Animals of fourth group were administrated with suspension of amiodarone 50 mg/kg through oral route for 7 days, on 7^{th} day, 6 hrs after the second dose of amiodarone in 2% acacia suspension of administration; the animals were fasted for 18 hrs. This fasting was continued till the end of experiments. However water supplied *ad libitum.* On 8th day 1 hr after the dose administration, after 60 min of respective treatment, pioglitazone 0.3 mg/kg, p.o. was administered to the same animals.

Animals of fifth group were administrated with suspension of amiodarone 50 mg/kg through oral route for 7 days, on 7th day, 6 hrs after the second dose of amiodarone in 2% acacia suspension of administration; the animals were fasted for 18 hrs. This fasting was continued till the end of experiments.

However water supplied *ad libitum.* On the 8thday 1 hr after the dose administration, after 60 min of respective treatment, nateglinide 50 mg/kg, p.o. was administered to the same animals.
Blood sample were withdrawn from the tail vein at intervals of 0, ½, 1, 2, 4, 8, 12, 18 and 24 hrs and analyzed for blood glucose concentration by GOD/POD method. Different methods based on the different properties of glucose are described for blood glucose estimation [15,16,17,18,19,20,21].
The percentage reduction in blood glucose levels at time„t" was calculated by using the following equation.

$$\%\ Blood\ sugar\ reduction\ at\ time\quad 't' = \frac{A-B}{A}\ X\ 100$$

Where, A = Initial blood glucose level before drug administration.
B = Blood glucose levels at time t" after the drug administration.
Same procedure was carried out for Diabetic rats.

RESULTS

Effect of Amiodarone pre-treatment on hypoglycemic effects of Pioglitazone and Nateglinide in healthy albino rats

Onset of hypoglycemia (time taken to reduce blood glucose level to the extent of 15- 20%), duration of hypoglycemia (time duration in which more than 15-20% reduction in blood glucose level is maintained) and peak hypoglycemia (i.e. maximum reduction in blood glucose level) were the parameters considered for the evaluation of influence on Pioglitazone and Nateglinide induced hypoglycemia. In this study the pre-treatment with of Amiodarone (50 mg/kg for seven days) has significantly enhanced the onset of hypoglycemia (i.e. from 2 hrs to 1 hr, i.e. 22.26±0.60%,22.03±2.78%, p< 0.001, p< 0.001), the peak hypoglycemia was enhanced significantly (i.e. 35.84±0.76% reduction before treatment and 47.04±2.01% reduction after treatment, p<0.001, p< 0.001) at 8th hr. However duration of hypoglycemia was increased from 18 hrs (22.01±0.78%, p< 0.001) before treatment to more than 24 hrs (21.94±2.74%, p< 0.001) after treatment induced by Pioglitazone.
The results of these findings are compiled in table No.1 & 2 and graphically depicted in figure No. 1.
The pre-treatment with of Amiodarone (50 mg/kg for seven days) has significantly enhanced the onset of hypoglycemia (i.e. from 1 hr to ½ hr, i.e. 20.50±1.96%, 22.13±1.05%, p< 0.001, p< 0.001), the peak hypoglycemia was enhanced significantly (i.e. 35.32±2.62% reduction before treatment and 47.64±1.99% reduction after treatment p<0.001, p< 0.001) at 4th hr. However duration of hypoglycemia was increased from 8 hrs (21.57±1.93%, p< 0.001) before treatment to more than 24 hrs (27.01±2.34% p< 0.001) after treatment induced by Nateglinide. These findings are recorded in table No.5& 26and graphically show in figure No. 2.

Table No. 1: Blood glucose levels with Pioglitazone (0.3mg/kg) in healthy albino rats before and after Amiodarone (50 mg/kg) treatment.

Time in hrs	Blood Glucose Levels (mg/dl) with Pioglitazone							Blood Glucose Levels (mg/dl) with Pioglitazone + Amiodarone.						
	1	2	3	4	5	6	Mean ± SEM	1	2	3	4	5	6	Mean ± SEM
0	87.78	96.77	81.03	77.45	72.67	99.53	85.87±4.38	118.3	94.59	98.36	109.5	101.3	96.89	103.2±3.69
½	79.54	90.01	73.65	73.72	69.03	94.58	80.09±4.13	110.6	79.23	82.56	97.89	86.29	80.32	89.48±5.04
1	74.65	82.00	67.83	65.73	66.74	85.73	73.78±3.46	106.5	65.59	76.39	83.26	80.59	72.88	80.87±5.71
2	67.94	73.79	63.73	61.92	56.73	75.75	66.64±2.97	91.23	51.79	56.33	62.29	63.22	56.03	63.48±5.81
4	61.00	65.72	56.73	55.62	50.64	67.45	59.53±2.61	82.59	50.56	51.72	56.29	58.83	54.39	59.06±4.86
8	56.72	59.92	52.17	51.29	47.88	61.62	54.93±2.18	73.52	48.93	50.86	52.33	50.82	52.02	54.75±3.78
12	63.99	68.12	60.11	57.73	53.01	68.34	61.88±2.47	81.01	59.36	61.59	55.31	57.12	64.39	63.13±3.86
18	69.83	75.37	63.28	60.00	58.26	74.35	66.85±3.00	105.5	62.89	65.02	60.33	64.89	67.78	71.07±6.96
24	79.73	87.01	72.68	69.93	67.53	90.52	77.90±3.84	107.9	71.50	75.39	80.01	79.39	71.31	80.92±5.60

Table No. 2: Percentage blood glucose reduction with Pioglitazone in healthy albino rats before and after Amiodarone treatment.

Time in hrs	Percentage Blood Glucose Levels (mg/dl) with Pioglitazone							Percentage Blood Glucose Levels (mg/dl) with Pioglitazone + Amiodarone.						
	1	2	3	4	5	6	Mean ± SEM	1	2	3	4	5	6	Mean ± SEM
½	9.38	6.98	9.10	4.81	5.00	4.97	6.70±0.86	6.31	16.23	16.60	10.62	14.81	17.10	13.61±1.74**
1	14.95	15.26	16.29	15.13	8.16	13.86	13.94±1.19	9.99	30.65	22.33	23.98	20.44	24.78	22.03±2.78**
2	22.60	23.74	21.35	20.05	21.93	23.91	22.26±0.60	22.94	45.24	42.73	43.12	37.54	42.71	39.05±3.38**
4	30.50	32.08	29.98	28.18	30.31	38.08	31.52±1.40	30.23	46.54	47.41	48.30	41.92	43.86	43.04±2.73**
8	35.38	38.07	35.61	33.77	34.11	38.08	35.84±0.76	37.90	48.27	48.29	52.22	49.83	46.31	47.14±2.01**
12	27.10	29.60	25.81	25.46	27.05	31.33	27.73±0.93	31.57	37.24	37.38	49.56	43.61	33.54	38.82±2.72**
18	20.44	22.11	21.90	22.52	19.82	25.29	22.01±0.78	10.83	33.51	33.89	44.91	35.94	30.04	31.52±4.61**
24	9.17	10.08	10.30	9.70	7.07	9.05	9.22±0.47	8.80	24.41	23.45	26.95	21.62	26.40	21.94±2.74**

Significant at p<0.01; ** highly significant at p<0.001; *** Very highly significant at p<0.0001

Effect of Amiodarone pre-treatment on antidiabetic activity of Pioglitazone and Nateglinide in diabetic rats:

Earlier experiments have revealed that Amiodarone pre-treatment has enhanced the hypoglycemic effect of pioglitazone and nateglinide in both carnivorous and herbivorous species. However in the present experiment the influence of amiodarone pre-treatment on same drugs under pathophysiological condition i.e. experimentally induced diabetes in albino rats was studied. It is evident from table No.16 and 17 that, the pre-treatment with of amiodarone (50 mg/kg for seven days) has significantly enhanced the onset of hypoglycemia (i.e. from 2 hrs to 1 hr, i.e. 31.07±3.15%, 22.14±1.93%, p< 0.001, p< 0.001), the peak hypoglycemia was enhanced significantly (i.e. 39.80±2.29% reduction before treatment and 52.92±1.45% reduction after treatment p<0.001, p< 0.001). However duration of hypoglycemia was increased from 18 hrs (27.22±2.46%, p< 0.001) before treatment to more than 24 hrs (22.99±0.39% p< 0.001) after treatment induced by Pioglitazone. The results are depicted in table No.3 & 4 and graphically shown in figure No.1.

The pre-treatment with of Amiodarone (50 mg/kg for seven days) has significantly enhanced the onset of hypoglycemia (i.e. from 1 hr to ½ hr, i.e. 25.66±0.64%, 20.99±0.96%, p<0.001, p< 0.001). Also the peak effect of hypoglycemia was enhanced significantly (i.e. 41.99±1.33% reduction before treatment to 51.60±1.56% reduction after treatment p< 0.001, p< 0.001) and duration of hypoglycemia was increased from 8 hr to more than to 24 hrs (i.e. 38.10 ± 0.51% before treatment and 21.72 ± 0.69% after treatment p< 0.001, p<0.001) induced by Nateglinide. The results are shown in table No. 6 & 7 and graphically shown in figure No. 2.

Table No. 3: Blood glucose levels with Pioglitazone (0.3mg/kg) in diabetic rats before and after Amiodarone (50 mg/kg) treatment.

Time in hrs	Blood Glucose Levels (mg/dl) with Pioglitazone							Blood Glucose Levels (mg/dl) with Pioglitazone + Amiodarone.						
	1	2	3	4	5	6	Mean ± SEM	1	2	3	4	5	6	Mean ± SEM
0	256.8	250.3	230.1	275.5	262.3	270.2	257.6±6.61	255.2	346.7	301.5	288.5	358.5	318.5	311.5±15.59
½	236.0	228.8	209.6	254.0	220.8	253.8	233.9±7.28	241.5	326.6	277.9	243.5	323.7	283.0	282.7±15.13
1	202.3	205.1	192.3	235.6	203.6	234.3	212.2±7.42	219.9	249.5	236.4	226.5	270.5	244.0	241.2±7.36
2	182.9	157.8	178.0	196.3	189.3	206.6	185.2±6.84	152.3	223.6	187.9	198.6	234.6	196.0	198.9±11.81
4	176.8	147.2	167.0	183.2	174.9	194.0	173.9±6.47	143.9	205.0	176.9	187.8	221.1	182.8	186.3±10.74
8	161.8	136.2	141.3	144.3	164.8	181.3	155.0±7.05	126.8	173.7	148.9	138.3	155.9	132.9	146.2±7.00
12	170.9	126.3	162.8	188.0	180.3	168.8	166.2±8.76	145.2	203.6	171.9	159.9	194.6	161.5	172.8±9.08
18	190.0	159.3	188.0	194.3	188.4	203.4	187.3±6.04	187.3	227.5	201.5	196.7	238.0	203.4	209.1±7.93
24	288.8	223.8	203.3	246.2	238.0	212.3	235.4±12.47	198.6	267.5	234.5	222.0	276.5	239.4	239.8±11.78

Table No. 4: Percentage blood glucose reduction with Pioglitazone in diabetic rats before and after Amiodarone treatment.

Time in hrs	Percentage Blood Glucose Levels (mg/dl) with Pioglitazone							Percentage Blood Glucose Levels (mg/dl) with Pioglitazone + Amiodarone.						
	1	2	3	4	5	6	Mean ± SEM	1	2	3	4	5	6	Mean ± SEM
½	8.0	8.7	8.8	7.8	15.83	6.06	9.19±1.38	5.36	5.79	7.81	15.59	9.70	11.14	9.23±1.56
1	21.22	18.08	16.40	14.48	22.37	13.28	17.64±1.48	13.83	28.03	21.59	21.48	24.54	23.39	22.14±1.93
2	28.76	36.95	22.64	28.73	27.81	23.52	28.07±2.08	40.31	35.49	37.66	31.13	34.55	38.46	36.27±1.33
4	31.14	41.17	27.42	33.54	33.31	28.83	32.57±1.98	43.59	40.87	41.30	34.90	38.30	42.59	40.26±1.29
8	36.98	45.59	38.55	47.61	37.16	32.90	39.80±2.29	50.29	49.87	50.60	52.03	56.50	58.24	52.92±1.45
12	33.44	49.52	29.24	31.78	31.23	37.52	35.46±3.03	43.07	41.26	42.97	44.56	45.70	49.28	44.47±1.14
18	26.01	36.64	18.29	29.49	28.16	24.71	27.22±2.46	30.11	34.37	33.16	31.81	33.61	36.13	33.20±0.84
24	10.90	10.60	11.61	10.73	9.27	21.40	12.42±1.82	22.17	22.82	22.22	23.04	22.86	24.82	22.99±0.39

Significant at p<0.01; ** highly significant at p<0.001; *** Very highly significant at p<0.0001

Figures No. 1: Percentage blood glucose reduction with Pioglitazone in healthy albino rats and Diabetic rats before and after Amiodarone treatment.

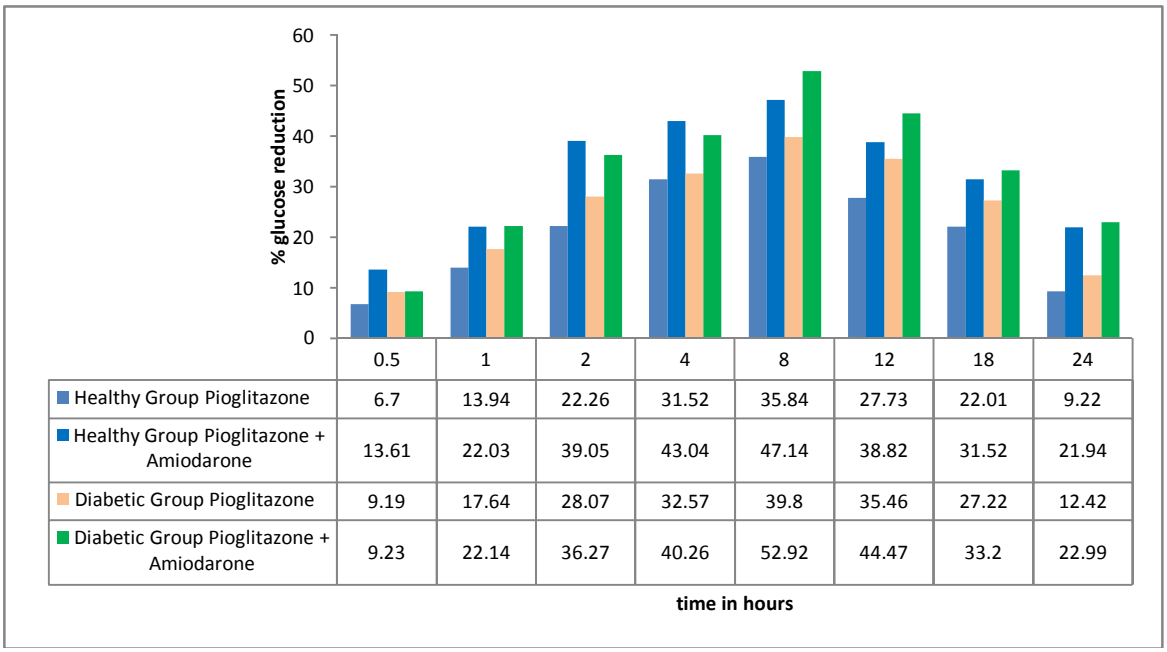


Table No. 5: Blood glucose levels with Nateglinide (50mg/kg) in healthy albino rats before and after Amiodarone (50 mg/kg) treatment.

Time in hrs	Blood Glucose Levels (mg/dl) with Nateglinide							Blood Glucose Levels (mg/dl) with Nateglinide + Amiodarone.						
	1	2	3	4	5	6	Mean ± SEM	1	2	3	4	5	6	Mean ± SEM
0	85.30	97.28	103.2	94.63	79.36	101.4	93.53±3.82	87.06	112.3	96.03	104.2	119.0	97.23	102.6±4.75
½	79.71	89.72	94.63	87.93	72.74	93.28	86.34±3.46	67.29	92.86	74.29	78.33	90.89	76.21	79.98±4.66
1	64.00	73.53	90.46	74.48	64.39	80.98	74.64±4.12	62.01	87.86	73.23	71.22	82.23	71.37	74.65±3.72
2	61.46	68.47	82.70	71.02	61.45	78.23	70.56±3.54	59.37	82.89	69.29	64.03	76.12	68.23	69.99±3.44
4	58.14	51.01	70.00	65.63	53.63	63.62	60.34±2.99	49.10	51.06	50.71	55.10	57.29	56.83	53.35±1.42
8	74.44	70.99	80.92	72.47	62.00	78.34	73.19±2.69	58.87	79.36	63.86	59.39	68.33	60.10	64.99±3.22
12	89.81	85.67	89.96	84.72	73.62	91.53	85.89±2.68	61.36	83.29	67.88	63.22	71.89	66.89	69.09±3.21
18	92.93	93.06	96.97	89.63	77.45	98.00	91.34±3.04	63.80	89.22	70.01	66.00	78.23	67.23	72.42±3.93
24	92.37	96.55	95.66	92.74	78.45	102.4	93.03±3.26	66.59	93.86	71.29	67.04	82.86	70.49	75.36±4.41

Table No. 6: Percentage blood glucose reduction with Nateglinide in healthy albino rats before and after Amiodarone treatment.

Time in hrs	Percentage Blood Glucose Levels (mg/dl) with Nateglinide							Percentage Blood Glucose Levels (mg/dl) with Nateglinide + Amiodarone.						
	1	2	3	4	5	6	Mean ± SEM	1	2	3	4	5	6	Mean ± SEM
½	6.55	7.77	8.30	7.08	8.34	8.07	7.68±0.29	22.70	17.35	22.63	24.84	23.62	21.61	22.13±1.05
1	24.97	24.42	12.34	21.29	18.86	20.13	20.50±1.96	28.77	21.80	23.74	31.67	30.89	26.59	27.24±1.60
2	27.94	29.61	19.86	24.94	22.56	22.90	24.64±1.48	31.80	26.22	27.84	38.56	36.03	29.82	31.71±1.95
4	31.84	47.56	32.17	30.64	32.42	37.30	35.32±2.62	43.60	54.53	47.19	47.12	51.85	41.55	47.64±1.99
8	12.73	27.02	21.58	23.41	21.87	22.79	21.57±1.93	32.37	29.36	33.49	43.02	42.57	38.18	36.50±2.30
12	-5.28	11.92	12.82	10.47	7.23	9.79	7.82±2.73	29.51	25.87	29.31	39.34	39.58	31.20	32.47±2.32
18	-8.94	4.33	6.03	5.28	2.40	3.41	2.08±2.26	26.71	20.59	27.09	36.67	34.26	30.84	29.36±2.37
24	-8.28	0.75	7.30	1.99	1.14	-0.96	0.32±2.06	23.51	19.13	25.76	35.80	30.36	27.50	27.01±2.34

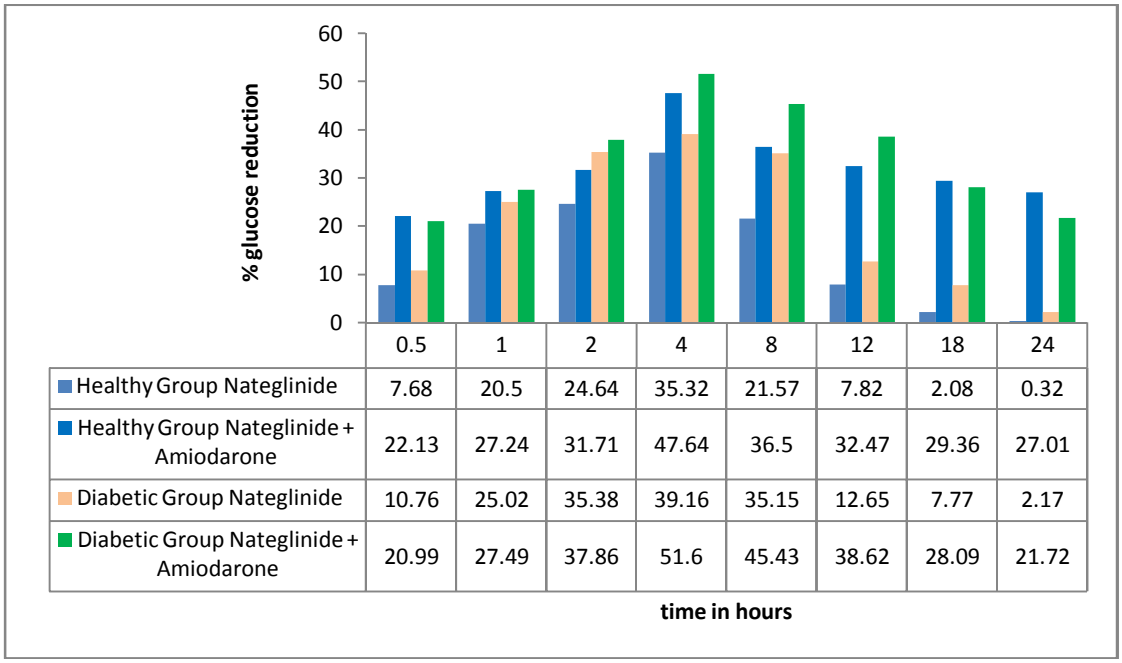
Table No. 7: Blood glucose levels with Nateglinide (50mg/kg) in diabetic rats before and after Amiodarone (50 mg/kg) treatment.

Time in hrs	Blood Glucose Levels (mg/dl) with Nateglinide							Blood Glucose Levels (mg/dl) with Nateglinide + Amiodarone.						
	1	2	3	4	5	6	Mean ± SEM	1	2	3	4	5	6	Mean ± SEM
0	256.8	267.3	245.6	250.6	277.5	260.3	259.7±4.70	389.0	261.9	336.0	380.8	367.5	282.6	336.3±21.72
½	277.1	239.8	222.7	225.1	248.6	226.8	240.0±8.45	322.0	199.4	268.0	301.0	288.0	219.4	266.3±19.54
1	191.0	200.6	189.4	182.2	204.9	190.6	194.6±2.65	302.5	172.0	242.9	288.0	263.6	202.5	245.3±20.53
2	156.5	173.7	161.2	147.4	171.6	160.7	167.8±4.09	236.0	160.0	214.8	237.0	233.6	172.5	209.0±14.01
4	144.8	163.7	151.9	132.8	159.9	150.7	157.7±4.48	201.8	129.7	179.7	176.8	162.0	126.7	162.8±12.11
8	159.0	167.8	152.3	152.7	176.4	157.9	168.4±6.69	234.7	148.0	185.0	189.0	201.5	143.6	183.8±13.94
12	214.6	244.0	218.1	211.0	246.3	227.4	226.9±6.20	245.6	169.0	219.5	208.0	224.5	167.7	205.7±12.82
18	225.8	252.5	232.9	232.8	251.9	240.5	239.4±4.47	287.1	187.0	230.0	273.9	264.7	208.0	241.8±16.22
24	242.9	263.7	242.1	250.0	274.5	250.7	254.0±5.18	200.7	207.1	262.8	309.0	286.4	214.6	246.8±18.65

Table No. 8: Percentage blood glucose reduction with Nateglinide in diabetic rats before and after Amiodarone treatment.

Time in hrs	Percentage Blood Glucose Levels (mg/dl) with Nateglinide							Percentage Blood Glucose Levels (mg/dl) with Nateglinide + Amiodarone.						
	1	2	3	4	5	6	Mean ± SEM	1	2	3	4	5	6	Mean ± SEM
½	11.56	10.27	9.30	10.17	10.41	12.86	10.76±0.51	17.23	23.82	20.24	20.94	21.64	22.08	20.99±0.96
1	25.63	24.94	22.87	23.78	26.15	26.76	25.02±0.60	22.23	34.32	27.70	24.36	28.26	28.08	27.49±1.68
2	39.06	35.01	34.86	26.95	38.15	38.26	35.38±1.83	39.30	38.88	36.07	37.77	36.43	38.73	37.86±0.55
4	43.59	38.74	38.14	30.01	42.37	42.08	39.16±2.02	48.11	50.47	46.51	53.57	55.92	54.99	51.60±1.56
8	38.09	37.19	37.95	21.36	36.42	39.91	35.15±2.79	39.66	43.48	44.93	50.36	45.16	48.99	45.43±1.57
12	16.42	8.69	11.18	15.80	11.21	12.60	12.65±1.21	36.85	35.48	34.66	45.38	38.90	40.43	38.62±1.61
18	12.08	5.52	5.17	7.08	9.20	7.59	7.77±1.04	26.20	28.59	31.55	28.08	27.97	26.14	28.09±0.80
24	5.4	1.35	1.41	0.2	1.08	3.6	2.17±0.79	22.94	20.92	21.77	18.86	22.06	23.78	21.72±0.69

Figures No. 2: Percentage blood glucose reduction with Nateglinide in healthy albino rats and Diabetic rats before and after Amiodarone treatment.



DISCUSSION

There are several reports that amiodarone inhibit the isoenzymes of CYP-450 enzyme system. The isoenzymes that are affected by amiodarone are CYP2C9, CYP3A4 and CYP2D6. There is a possibility that drug- drug interaction may occur between the amiodarone and the drugs metabolised by these enzymes. Pioglitazone and nateglinide are metabolised by CYP2C9 and CYP3A4[7 ,8].

It was observed in all the two types of animals i.e. healthy rats and diabetic rats that, drug-drug interaction occur, when amiodarone, pioglitazone and nateglinide are administered concomitantly. Since the amiodarone has shown significant effect on onset of hypoglycemia, it may be inferred that amiodarone interferes with absorption of oral antidiabetic agents. However amiodarone have significantly enhanced the hypoglycemia in both induced by pioglitazone and nateglinide. This may be due to fact that amiodarone mainly inhibit CYP2C9 and CYP3A4[6], which is involved in the metabolism of pioglitazone and nateglinide.

It is evident from the findings of the results that pre-treatment with amiodarone (50 mg/kg for seven days) has significantly decreased the onset of hypoglycemia (i.e. from 2 hr to 1 hr, i.e. 22.26±0.60, 22.03±2.78, $p<0.001$), significantly enhanced the peak hypoglycemia (35.84±0.76% before treatment and 47.04±2.01% after treatment, $p<0.001$) at 8th hr and duration of hypoglycemia was also significantly enhanced from 18 hrs to more than 24 hrs (i.e. 22.01±0.78, 21.94±2.74, $p<0.001$) induced by pioglitazone (Table No. 4 and 5, Figure No. 4). Whereas, pre-treatment with amiodarone (50 mg/kg for seven days) has significantly altered the onset of hypoglycemia (i.e. from 1 hr to ½ hr, i.e. 20.50±1.96, 22.13±1.05, $p<0.001$), significantly enhanced the peak hypoglycemia (35.32±2.62% before treatment to 47.64±1.99% after treatment, $p<0.001$) at 4th hr and duration of hypoglycemia was also significantly enhanced from 8 hrs to more than 24 hrs, (i.e. 21.57±1.93 to 27.01±2.34, $p<0.001$) induced by nateglinide

CONCLUSION

Amiodarone single dose treatment has not influenced the blood glucose levels in healthy albino rats and diabetic rats. These findings are indicating that amiodarone does not possess hypoglycaemic activity therefore it may be inferred that drug-drug interaction with pioglitazone and nateglinide is a pharmacokinetic type.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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