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ORIGINAL ARTICLE

A Study on effect of Amiodarone on the Pharmacokinetic of Repaglinide in Diabetic animal

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ABSTRACT
The effect of one drug may be altered by concurrent administration of another drug. Such drug interactions are sometime of major clinical importance and may be very serious and even deleterious to the patients. According to International Diabetes Federation (IDF) the enormity of the Diabetes mellitus epidemic, disease, now affects as staggering 246 million people worldwide, with 46% of all those affected in the 40-59 age group and the total number of people living with diabetes will skyrocket to380 million within 20years if nothing is done. Our information shows that causes of cardiac arrhythmia are related to diabetes or a family history of diabetes. In such patients, various anti-arrhythmic drugs are given along with oral hypoglycemic agents for a specific period. Amiodarone is a widely using anti-arrhythmic drug to treat cardiac arrhythmia. Amiodarone is metabolized by Cytochrome P450 enzymes and isoenzymes CYP2C9 and CYP3A4 are responsible for its metabolism. Amiodarone is strong inhibitor of isoenzymes CYP2C9 and CYP3A4. Similarly antidiabetic agents like repaglinide are metabolized by isoenzymes CYP2C9 and CYP3A4. Therefore there may be every possibility of drug interaction of amiodarone with repaglinide. However there are no reports that the drug interactions studies with amiodarone and antidiabetic agents like repaglinide. Hence, the present study is planned to understand the possible drug-drug interaction between repaglinide along with amiodarone. The whole study was divided into three phases, in the first phase; the influence of repaglinide (50mg/kg) on the blood glucose levels in healthy rats were established. In the second phase the influence of pre-treatment of amiodarone (50 mg/kg per day) on the hypoglycaemic activity of above mentioned anti-diabetic drugs were studied in healthy albino rats. In final phase of the study, diabetic rats were used to find out the drug-drug interactions of Amiodarone and oral antidiabetic drugs in pathophysiological conditions. Oral dose of amiodarone has enhanced the onset of action, duration of action and peak effect in healthy rats, and diabetic rats. The potentiation of hypoglycemic effect is may be due to the inhibition of CYP2C9 and CYP3A4 isoenzymes system by amiodarone pre-treatment, suggesting the requirement of therapeutic Drug Monitoring when these drugs are used concomitantly.
Keywords: *Amiodarone, repaglinide, hypoglycemic agents, drug-drug interaction, antidiabetic activity, Cytochrome P450*

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INTRODUCTION

Drug-drug interactions (DDIs) are concern for patients and providers, as multiple medication use becoming more common to manage complex diseases. The consequences of DDIs can range from noun toward effects to drug-related morbidity and mortality. Although DDIs are considered preventable medication- related problems, studies have found that up to 11% of patients experience symptoms associated with DDIs and DDIs are responsible for up to 2.8% of hospital admissions.[1] Patients have many concerns when multiple medications are started, including prescribing errors, the cost of medications and possible adverse effects. Significantly, 58% of patients worry that they will be given medications that have drug interactions that will adversely affect their health. [2]

People with diabetes also tend to develop heart disease or have strokes at an early age than other people and required long therapy. [3] There are certain patients who may be suffering with more than one disease like diabetes mellitus and arrhythmia or cardio vascular diseases simultaneously during that specified period. There is a possibility that drug-drug interaction may occur during that time. Hence in

such cases it is required to adjust dosage regimen and frequency of administration of one or all drugs, which are to be administered simultaneously. [4]

In such cases, anti-arrhythmic agents are commonly prescribed as anti- arrhythmic and for other related cardiovascular complications. So there is always a need for administration of antiarrhythmic agents like procainamide, lidocaine, propranolol, digitalis etc. along with oral antidiabetic. [5]

Amiodarone is one such anti-arrhythmic agent which is inhibitor of CYP2D6, CYP1A2, CYP3A4,CYP3A5, CYP3A7 and CYP2C9 enzyme system.[6] Here antidiabetic drugs like Repaglinide metabolized 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 repaglinide is not reported.

Hence, the present study is planned to understand the possible drug-drug interaction between hypoglycemic agents like repaglinide 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 repaglinide, when they are used simultaneously. Therefore the study is to assess the possibility of potential interaction of repaglinide with amiodarone is very much needed.

MATERIALS AND METHODS

Animals:

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.

NORMAL ALBINO RATS

The normal albino rats of either sex were divided into four groups of six each. All the rats weighing between 160 to 180gm were used.

DIABETIC RATS

Induction of diabetes: [11]

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 [12]

Oral feeding administration was done by oral feeding needle and 1 ml glass syringe.

Method for blood sampling [13, 14, 15]

The rat was anesthetized by anesthetic ether in anesthetic chamber. After that small anesthetized rat was taken up from anesthetic 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).

Estimation of blood glucose:

Enzyme, GOD-POD endpoint colorimetry [16]

The GOD/POD method was used for *in vitro* quantitative determination of glucose in serum/plasma or cerebrospinal fluid.[17] .

Experimental procedure:

Group of six albino rats of either sex weighing between 160-180 gm were selected for the study. The animals were randomly distributed into 3 groups (n=6, I, II, III); each group was consisting of 6 animals. Group of six rats were given different drugs orally, as follows:

Three groups (n=6) of animals were selected (I, II, III)

Group I: Received repaglinide (50 mg/kg) [9]

Group II: Received Amiodarone (50mg/kg) [10]

Group III: were treated with amiodarone (50mg/kg) for 7 days with regular feeding and on 8th day one hr after amiodarone treatment the animals of group III were administered with repaglinide (50mg/kg).

The blood samples were collected from tail vein from rats and blood glucose levels were analyzed so as to attain the influence of pre-treatment of amiodarone on hypoglycemia induced by repaglinide. The same method was repeated with amiodarone(50mg/kg) and repaglinide (50mg/kg) on diabetic rats with same dose of these three drugs as used in healthy rats.

Then the anti-diabetic activity of repaglinide at time "t" was calculated and the % blood glucose reduction at various time intervals were calculated before and after amiodarone treatment.

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

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 Repaglinide in healthy albino rats:

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. 22.35±1.96%, 23.74±1.05%, p< 0.001, p< 0.001), the peak hypoglycemia was enhanced significantly (i.e.37.00±2.62% reduction before treatment and 49.30±1.99% reduction after treatment p<0.001, p< 0.001)at 4th hr. However duration of hypoglycemia was increased from 8 hrs (23.22±1.93%, p< 0.001) before treatment to more than 24 hrs (28.51±2.34% p< 0.001) after treatment induced by Repaglinide. These findings are recorded in table No.1 and 2.

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

Time in Hrs	Blood Glucose Levels (mg/dl) with Repaglinide							Blood Glucose Levels (mg/dl) with Repaglinide + Amiodarone						
	1	2	3	4	5	6	Mean± SEM	1	2	3	4	5	6	Mean± SEM
00	87.33	95.88	106.2	96.69	81.54	103.4	95.13±3.82	86.16	114.6	98.13	105.1	117.01	99.33	103.39±4.75
½	81.76	92.45	96.66	89.98	71.76	95.22	87.97±3.46	69.32	93.56	75.32	80.30	91.81	77.21	81.25±4.66
1.0	65.50	75.55	91.48	75.50	66.45	82.82	76.21±4.12	64.23	89.84	72.35	74.12	81.27	73.24	75.84±3.72
2.0	63.40	67.57	84.36	72.13	63.48	79.53	71.74±3.54	61.13	84.83	67.21	65.33	78.23	69.42	71.02±3.44
4.0	59.44	52.23	71.50	67.83	55.67	66.22	62.14±2.99	51.15	53.26	52.51	56.16	59.59	58.45	55.18±1.42
8.0	72.54	72.54	82.12	74.48	65.00	76.84	73.92±2.69	56.85	77.66	61.85	57.49	70.93	63.15	64.65±3.22
12.0	91.85	88.60	88.86	86.76	75.52	93.56	87.52±2.68	63.38	85.39	69.66	65.62	73.77	68.49	71.05±3.21
18.0	94.63	95.17	98.66	90.53	79.48	99.50	92.99±3.04	65.85	91.02	72.08	67.05	79.73	69.15	74.14±3.93
24.0	90.57	94.35	93.68	93.62	77.45	104.40	93.34±3.26	68.50	95.81	73.25	69.14	84.80	74.49	77.66±4.41

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

Time in Hrs	Percentage Blood Glucose Levels (mg/dl) with Repaglinide							Percentage Blood Glucose Levels (mg/dl) with Repaglinide + Amiodarone						
	1	2	3	4	5	6	Mean±SEM	1	2	3	4	5	6	Mean±SEM
½	8.45	9.62	7.89	9.58	10.23	10.05	9.30±0.29	25.27	18.13	24.73	26.34	25.32	22.67	23.74±1.05
1.0	27.47	25.40	15.30	23.21	19.36	22.35	22.18±1.96	26.76	22.50	21.54	30.45	29.49	25.34	26.06±1.60***
2.0	25.64	28.31	18.55	22.84	21.50	21.80	23.10±1.48	33.40	25.42	29.54	39.41	37.08	31.02	32.64±1.95***
4.0	33.54	48.86	33.67	32.60	35.02	38.35	37.00±2.62	45.10	57.41	49.08	48.16	52.92	43.15	49.30±1.99***
8.0	15.53	28.14	23.55	22.45	24.87	24.79	23.22±1.93	31.86	30.16	35.67	45.82	43.62	39.78	37.81±2.30***
12.0	-7.30	14.82	15.63	12.04	9.23	10.70	9.18±2.73	28.87	27.47	30.41	38.74	39.98	34.25	33.28±2.32***
18.0	-9.97	5.36	8.08	6.68	4.45	5.21	3.30±2.26	28.41	22.43	28.09	37.69	35.21	32.92	30.79±2.37***
24.0	-9.46	1.85	9.36	3.97	3.24	-0.98	1.33±2.06	25.56	18.45	28.36	37.85	31.31	29.55	28.51±2.34***

*Significant at p<0.01; ** highly significant at p<0.001; *** Very highly significant at p<0.00

Effect of Amiodarone pre-treatment on antidiabetic activity of Repaglinide in diabetic rats:
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. 26.22±0.64%, 22.52±0.96%, p< 0.001, p< 0.001). Also the peak effect of hypoglycemia was enhanced significantly (i.e. 40.72±1.33% reduction before treatment to 53.11±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. 36.27 ± 0.51% before treatment and 26.23 ± 0.69% after treatment p< 0.001, p<0.001) induced by Repaglinide. The results are shown in table No. 3 & 4

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

Time in Hrs	Blood Glucose Levels (mg/dl) with Repaglinide							Blood Glucose Levels (mg/dl) with Repaglinide + Amiodarone						
	1	2	3	4	5	6	Mean±SEM	1	2	3	4	5	6	Mean±SEM
00	258.1	268.1	247.1	252.6	278.8	262.1	261.17±4.70	389.9	263.1	337.2	382.2	368.9	283.5	337.52±21.72
½	278.1	240.4	224.0	226.4	249.6	227.5	241.03±8.45	324.1	199.9	269.3	303.7	289.6	219.4	267.71±19.54
1.0	193.8	202.7	190.8	184.6	205.6	192.4	194.98±2.65	304.4	174.2	243.6	289.5	264.4	204.4	246.75±20.53
2.0	158.6	174.9	164.0	148.6	172.5	161.8	163.4±4.09	237.6	162.6	215.9	238.6	235.8	173.7	210.7±14.04
4.0	150.9	164.5	157.3	134.2	166.5	120.4	152.3±4.48	203.9	130.8	180.9	178.6	163.6	127.8	164.26±12.11
8.0	160.2	168.9	154.6	154.2	178.8	158.3	162.5±6.69	236.3	149.9	187.5	190.5	203.7	145.7	185.6±13.94
12.0	215.5	245.7	219.9	213.3	247.5	229.2	228.51±6.20	246.9	170.5	220.8	210.7	226.3	168.8	207.33±12.82
18.0	227.4	253.6	234.7	234.2	253.0	243.0	240.98±4.47	289.2	188.3	231.5	274.7	266.9	209.9	243.41±16.22
24.0	243.6	264.8	243.6	252.2	275.9	251.8	255.48±5.18	202.3	208.6	264.5	310.1	287.8	216.2	248.25±18.65

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

Time in Hrs	Percentage Blood Glucose Levels (mg/dl) with Repaglinide							Percentage Blood Glucose Levels (mg/dl) with Repaglinide + Amiodarone						
	1	2	3	4	5	6	Mean±SEM	1	2	3	4	5	6	Mean±SEM
½	14.50	11.57	9.98	12.08	11.51	14.26	12.31±0.51	18.30	25.42	22.14	21.54	23.74	24.01	22.52±0.96***
1.0	26.53	25.84	23.47	25.89	27.65	27.96	26.22±0.60	24.13	35.82	28.25	26.76	29.66	29.18	28.96±1.68***
2.0	40.46	37.06	35.56	27.65	39.85	39.76	36.72±1.83	41.30	39.58	37.77	39.07	37.83	39.13	39.11±0.55***
4.0	45.79	39.84	39.44	32.51	43.57	43.18	40.72±2.02	49.12	53.05	47.55	55.57	56.52	56.89	53.11±1.56***
8.0	39.50	38.99	38.75	22.06	37.62	40.71	36.27±2.79	40.67	45.54	45.83	52.45	46.86	49.78	46.85±1.57***
12.0	18.40	9.76	12.54	16.85	13.24	14.65	14.24±1.21	38.35	36.67	35.68	47.78	39.93	42.03	40.07±1.61***
18.0	14.18	6.72	7.37	8.88	9.94	8.69	9.29±1.04	28.20	28.99	33.03	29.18	28.93	27.43	29.29±0.80***
24.0	7.25	2.46	2.46	1.22	2.48	4.16	3.33±0.79	24.63	21.69	23.88	19.97	42.02	25.23	26.23±0.69***

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

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. Repaglinide are metabolised by CYP2C9 and CYP3A4 [7, 8]. Hence, there is a possibility of development of drug-drug interaction between these two types of therapeutic agents. There are no reports regarding the interaction of these drugs but those are not enough to confirm the interaction. Hence, in the present study repaglinide is oral antidiabetic agents and amiodarone is a Class III anti-arrhythmic agent are being used to understand, evaluate and confirm the drug-drug interaction between them.
It was observe that all the two types of animal's i.e. healthy rats and diabetic rats that, drug-drug interaction occur, when amiodarone and repaglinide 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 induced by repaglinide. This may be due to fact that amiodarone mainly inhibit CYP2C9 and CYP3A4, which is involved in the metabolism of repaglinide.
The above observations suggest that the interaction between amiodarone and oral antidiabetic agents are very intense and it demands there adjustment of dose and frequency of oral antidiabetic agents when they are used concomitantly.

CONCLUSION:
From the study it is indicated that the isoenzymes of CYP450 system that are responsible for the metabolism of repaglinide are sensitive to amiodarone and hence therapeutic dose of it could inhibit the isoenzymes and thereby affect the hypoglycemia induced by repaglinide. Therefore it seems there is a need to go for therapeutic drug monitoring (TDM) so as to readjust the dose and frequency of administration of repaglinide, when they are used with amiodarone.

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CONFLICTS OF INTEREST
The authors declare no conflict of interest.

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