Effect of Amiodarone on Rosiglitazone's Pharmacokinetics in animal model

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ABSTRACT:

Aim: The current research looked to determine the impact of amiodarone, an antiarrhythmic medication, administered in multiple doses over the course of seven days on the hypoglycaemic action of rosiglitazone in normal and diabetic rats. **Objective:** The goal of the research was to identify the drug interaction between rosiglitazone and amiodarone in normal and diabetic rats. **Method:** These studies were conducted in six healthy and six diabetic rats of both sexes and the dose of the administered drugs was rosiglitazone 0.3 mg/kg and amiodarone 50 mg/kg body weight. The medication was ingested through the oral route. At predetermined intervals, blood samples were drawn from the tail vein, and a semi-autoanalyser was used to determine the amount of glucose by employing the GOD/POD method. **Result:** The findings showed that amiodarone, an antiarrhythmic medication, influenced the hypoglycaemic activity of rosiglitazone when given alone and in combination with rosiglitazone in normal and diabetic rats. **Conclusion:** According to this research, when amiodarone and rosiglitazone are used together, monitoring of the therapeutic drug is necessary for modifying the therapeutic dose.

KEYWORDS:

Amiodarone, drug-drug interactions, GOD/POD method, rosiglitazone, antiarrhythmic.

INTRODUCTION:

Rosiglitazone is a novel insulin-sensitizing, oral antidiabetic agent of the thiazolidinedione class, used in the treatment of patients with Type 2 diabetes mellitus, and is an effective and well-tolerated agent for lowering blood glucose [1, 2]. It is metabolized through *N*-demethylation and *p*-hydroxylation, mainly by CYP2C8 and to a lesser extent CYP2C9 [3], and does not undergo enterohepatic recirculation [3, 4]. In addition to antidiabetic drugs, many other drugs may be prescribed to treat comorbidities in diabetic patients, which may result in drug interactions [5]. Amiodarone was initially developed in the early 1960s as a treatment for angina pectoris since it produces coronary vasodilation and decreases cardiac oxygen demand. However, its pronounced antiarrhythmic effects redirected its use and amiodarone has become a widely used class III anti-arrhythmic drug. Compared to other antiarrhythmic drugs, it is more effective in treating both supraventricular and ventricular arrhythmias.[6] Amiodarone is a Class III antiarrhythmic agent [7, 8] that prolongs the duration of action potential and hence increases the refractory period of atrial, nodal and ventricular tissues, thereby having a very broad spectrum of activity [9].

Amiodarone is subject to multiple interactions with oral anticoagulants (e.g., Warfarin) and any drugs that cause bradycardia, e.g., beta blockers and calcium channel blockers. Amiodarone increases Digoxin level [8, 10]. Drugs that deplete potassium from the body (e.g., diuretics) should be avoided at the time of treatment with this drug. Amiodarone may increase Phenytoin levels [8, 11].

Thus, the present study's goal is to determine if hypoglycemic medicines like rosiglitazone and anti-arrhythmic agent like amiodarone interact with one another in healthy rats and diabetic rats. The effect of amiodarone on rosiglitazone at the onset, duration, and peak of hypoglycemia are the basic limits investigated for the interaction between the medicines previously mentioned. rosiglitazone and amiodarone may interact, and more research is required to determine if this is the case.

MATERIAL AND METHODS:

Studies were carried out in the Department of Pharmacology in DCS's ARA College of Pharmacy, Mumbai-Agra Road, Nagaon, Dhule-424006, Maharashtra, which is dually licensed by the CPCSEA with the registration number (1367/PO/Re/S/10/ CPCSEA). The study protocol number ARACOP/IAEC0/20/5 was accepted according to existing regulations of CPCSEA by the Institution Animal Ethics Committee (IAEC) in its meeting,

Animals:

We used a total of 12 rats (both gender) for this investigation obtained from the LACSMI BioFarms, Ale Phata, Pune, Maharashtra. (Registration number 1277/PO/RcBt/S/09 /CPCSEA).

Method for oral administration [12]:

A glass syringe and oral feeding needle were used to administer the drug.

Method for blood sampling [13, 14, 15]:

The rats were put in a sedative chamber and given sedative ether to put them to sleep. By giving a gentle massage on the tail and with the help of xylene the tail vein is widened, then its tip is cut off and blood is collected with an anticoagulant mixture in epindroff tubes.

Estimation of blood glucose [16, 17]:

GOD/POD methodology was employed as one of the most accurate, easy, step-by-step, fast, trustworthy and acceptable.

EXPERIMENTAL PROCEDURE

Healthy Albino Rats:

6 rats, weighing between 150 to 180 grams, were used in the experiment. They had been marked for easy tracing. The animals were kept in colony cages according to industry standards. On the day before the experiment, the food was taken away 18 hours in advance of the start time. However, unlimited access to water was granted. The fasting lasted for the duration of the experiment. The following blood sample was taken from the tail vein of each rat for examination to guarantee the baseline glucose level. Then, in the first part of the study, the animals were administered rosiglitazone 0.3 mg/kg in 2% gum acacia suspension orally. At 0, 0.5, 1, 2, 4, 6, 8, 12, 18 and 24 hours, blood was drawn from the tail vein and tested with GOD/POD method. In the second part of the study, after the sufficient washout period, the same animals were used and amiodarone 50 mg/kg in 2% gum acacia suspension was given for 7 continuous days, The rats are starved on the 7^{th} day after giving amiodarone. The fasting lasted until all of the results were in. On the eighth day, one hour after receiving amiodarone 50 mg/kg, the same animals received rosiglitazone 0.3 mg/kg. The collection of samples of blood is done at the above same time intervals and analyzed for determining the glucose concentration.

Diabetic Rat:

The efficacy of anti-diabetic drugs in pathological situations such as diabetes mellitus is also unknown in rats when amiodarone is used. Diabetic rats will be used as test subjects in the current research to illustrate this perspective.

Induction of diabetes [18, 19]:

Rats of both sexes were used to induce diabetes. The intraperitoneal method was utilised to give 100 mg/kg of newly prepared alloxan monohydrate, followed the following day by 50 mg/kg of body weight. Next, 10 % dextrose was administered to prevent hypoglycemia from occurring right away. The diabetic rats were defined as those with fasting blood glucose levels greater than 250 mg/dL and were enrolled in the experiment.

Experimental procedure:

The same procedure is employed in diabetic rats as the above in healthy rats for the estimation of blood glucose levels.

Statistical analysis:

The student-paired "t-test" was used to analyse the results. The level of statistical significance was defined as P values under 0.05.

RESULTS:

Amiodarone pre-medication effect on rosiglitazone hypoglycemic effect in healthy rats:

The onset of hypoglycemia was significantly altered by pre-medication with amiodarone (50 mg/kg) in this trial (19.48±0.51% pre-medication to 28.46±0.57% rises post-medication at 1st hour), peak hypoglycemia was substantially risen (45.08±0.89% pre-medication to 59.92±0.48% post-medication at 8th hour. Hypoglycemia persisted for 18 hrs during pre-medication at 19.43±0.88% and 26.82±2.58% post-medication at 24 hours. Table 1 provides the findings.

Table No. 1: % of glucose levels in healthy rats pre and post-medication with rosiglitazone (0.3 mg/kg) and amiodarone (50 mg/kg).

Time in hr	(A) glucose levels (mg/dl)	(R) glucose levels (mg/dl)	(A+R) glucose levels (mg/dl)
	Mean ± SEM	Mean ± SEM	Mean ± SEM
0	-	-	-
½	1.34±0.11	8.50±0.52	19.10±0.63***
1	2.54±0.15	19.48±0.51	28.46±0.57***
2	3.11±0.11	25.56±0.69	35.85±0.69***
4	4.34±0.17	33.36±0.61	43.68±0.70***
6	5.52±0.14	38.52±0.84	49.99±0.49***
8	6.43±0.06	45.08±0.89	59.92±0.48***
12	4.97±0.17	32.36±0.60	49.10±0.61***
18	3.98±0.16	19.43±0.88	36.55±0.52***
24	3.05±0.17	9.23±0.74	26.82±2.58***

A + R: Amiodarone + Rosiglitazone;

Mean±SEM; *** Significant at P<0.001; ** Significant at P<0.01; * Significant at P< 0.05 compared to rosiglitazone control for n = 6

The impact of pre-medication with amiodarone on the anti-diabetic actions of rosiglitazone in diabetic rats:

The hypoglycemic impact of rosiglitazone is increased by amiodarone pre-treatment in healthy albino rats. As a result of this experiment, the impact of amiodarone pre-treatment on rosiglitazone was examined in rats that had been artificially caused to develop diabetes. The onset of hypoglycemia was increased significantly by pre-treatment with amiodarone 50 mg/kg (pre- medication 18.26±0.46% to 25.06±0.40% raised after treatment at 1st hour), peak hypoglycemia was substantially risen (pre-medication 45.70±0.43% to 53.88±0.58% post-medication at the 8th hour). Hypoglycemia persisted for 18 hours during pre-medication at 20.42±0.57% and increased to 18.75±0.49% post-medication at 24 hours. Table 2 shows the results.

Table No. 2: % of glucose levels in diabetic rats pre and post-medication with rosiglitazone (0.3 mg/kg) and amiodarone (50 mg/kg).

Time in hr	(A) glucose levels (mg/dl)	(R) glucose levels (mg/dl)	(A+R) glucose levels (mg/dl)
	Mean ± SEM	Mean ± SEM	Mean ± SEM
0	-	-	-
½	1.26±0.05	8.77±0.37	16.93±0.32***
1	2.29±0.06	18.26±0.46	25.06±0.40***
2	3.63±0.05	26.23±0.49	31.97±0.53***
4	4.61±0.06	33.92±0.61	36.77±0.52***
6	5.89±0.10	38.94±0.36	43.83±0.50***
8	6.66±0.07	45.70±0.43	53.88±0.58***
12	6.08±0.05	33.36±0.53	41.62±0.61***
18	4.72±0.11	20.42±0.57	28.20±0.72***
24	3.43±0.06	10.15±0.39	18.75±0.49***

A + R: Amiodarone + Rosiglitazone;

Mean±SEM; *** Significant at P<0.001; ** Significant at P<0.01; * Significant at P< 0.05 compared to rosiglitazone control for n = 6

DISCUSSION:

The onset, duration and peak hypoglycemic effect (the amount of time it takes for blood glucose levels to stay at their lowest level i.e., 15%) were all taken into account when determining the effectiveness of the hypoglycemic result.

Amiodarone has been reported to inhibit the CYP1A2, CYP2C9, CYP2D6, and CYP3A4 enzymes, raising the chance that inhibitory metabolites have a more direct impact compared to its parent medication [20, 21].

According to these findings, amiodarone has no hypoglycemic impact, indicating that rosiglitazone and amiodarone have a pharmacokinetic type of drug interaction. The onset of hypoglycemia with rosiglitazone was increased in healthy albino rats treated with amiodarone for one week, although peak hypoglycemia and hypoglycemic duration were both enhanced. Furthermore, in diabetic rats, one week of amiodarone pre-treatment increased hypoglycemia's onset while increasing its peak and duration when combined with rosiglitazone. To determine the impact of amiodarone pretreatment on the pharmacokinetic properties of rosiglitazone in humans, additional research is required.

CONCLUSION:

This research indicates that the simultaneous dosing of rosiglitazone as an antidiabetic agent and amiodarone as an antiarrhythmic agent shows that amiodarone potentiates the hypoglycemic action of rosiglitazone in both healthy and diabetic rats. This data suggests that when rosiglitazone and amiodarone are taken simultaneously, blood glucose monitoring is necessary. When amiodarone is used with oral antidiabetic medicines, the dosage and frequency of these medications should be changed as well.

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