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Original Article

Effect of Multi Drug Administration on Cardiac Enzymes and Tissues

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ABSTRACT

In the present study individual and combinations of drugs were given to rabbits for the period of 60 days and their effects on cardiac function and myocytes were observed.
Results shows that as compared to control rabbits, administration of acarbose, glibenclamide individually and GLoAt combination showed highly significant increase ($p < 0.005$) in CK. The animals received Losartan individually showed highly significant decrease ($p < 0.005$) in CK. Animal received Atorvastatin showed significant decrease in CK ($p < 0.05$) while animal received MAAt combination showed significant increase in CK ($p < 0.05$). Similarly with respect to control, animals received Metformin showed significant increase ($p < 0.05$) in GOT level and highly significant increase ($p < 0.005$) in animals received combination GLoAt.

Keywords: Cardiac Myocytes, Cardiac Toxicity**,** Cardiomyopathy, Atrial Fibrillation, Glutamic-Oxaloacetic Transaminase, Creatinine kinase.

INTRODUCTION

Most of the drugs having potential to induce cardiac toxicity results in serious life threatening problems. We can classify cardio toxic effects as predictable and less predictable effects[1]. All those undesirable adverse cardiac effects induced by cardio active agents like digoxin induced arrhythmias are termed as predictable effect. However, cardiac adverse effect induced by non cardiovascular agents like doxorubicin induced cardio toxicity or heart failure are termed as less predictable effects. Table 1 summarizes the name of different drugs inducing cardiovascular toxicity [2-4].
Some of the drugs Cisapride, Clarithromycin, Erythromycin, Fluconazole should not been taken with terfenadine as there is possible chance of prolongation of QT interval. Terfenadine is completely metabolized in the liver and further increase the chance of severe cardiac toxicities [5].

MATERIALS AND METHODS

This study was conducted in the Department of Pharmacology, Faculty of Pharmacy, University of Karachi, Karachi, after approval of the proposal from the Board of Advance Study and Research (BASR), University of Karachi. The Departmental research committee of Pharmacology permitted the use of animals in this experiment in accordance with the guidelines of NACLAR[7] and National Institute of Health (NIH) for use of laboratory animals[8].

All animals were divided in eleven groups, each comprising of 10 animals. One group served as control which was given normal saline equivalent to the volume of respective doses according to their body weight[9].

7 groups were given acarbose, glibenclamide, metformin, lisinopril, losartan, atorvastatin and amlodipine individually and remaining 3 groups were given drugs in combination (which are most commonly prescribed by doctors) i.e. acarbose, lisinopril and atorvastatin (GlLAt); Glibenclamide, losartan and atorvastatin (GLoAt) and metformin, amlodipine and atorvastatin (MAAt). All drugs were given in normal therapeutic doses (Acarbose = 8.57, Glibenclamide = 0.21, Metformin = 42.85, Lisinopril = 1.1, Losartan = 1.4, Atorvastatin = 1.1, Amlodipine = 0.1) in mg/kg as per body weight.

Blood samples of 5 ml were collected at the end of dosing period i.e. 60 days through cardiac puncture in gel tube for biochemical assays of cardiac enzymes i.e. glutamic oxaloacetic transaminase (GOT) and creatinine kinase (CK). GOT in the serum was estimated by kinetic method with reference to the International Federation of Clinical Chemistry[10] and CK was estimated by Humazym M-Test[11].

Microscopic Histological Examination

Specimens of heart after removal from body were preserved in 10% buffered formalin for at least 24 hr to prevent actual morphology, autolysis, bacterial decay and to provide slight hardness. Tissue sections were stained for routine histological examination.

Statistical Analysis

All values were compared with control by taking mean and standard error to the mean using two-way analysis of variance (ANOVA) followed by post hoc. Data was reported as mean ± standard error to the mean with 95% confidence interval and p-values were observed. Values of $P<0.05$ were considered as significant and $P<0.005$ as highly significant[12].

RESULTS

Table 2 shows the comparison of CK and GOT levels among control animals and animals kept on individual drugs and their combinations for 60 days.

Animals received acarbose and glibenclamide alone revealed a highly significant increase in CK level i.e. 412.2±2.59 µ/l and 308.9±3.54 µ/l with respect to control i.e. 205.35±6.98 µ/l, on contrary animals received losartan and atorvastatin alone revealed a highly significant decrease and significant decrease in CK levels i.e. 112.06±0.59 µ/l and 172.92±6.12 µ/l as compare to control. However the same groups did not show any significant alteration in GOT level at the end of dosing.

Animals kept on metformin alone revealed significant increase in GOT level i.e. 84.48±4.89 µ/l with respect to control i.e. 42.80±0.75 µ/l, without any significant alteration in CK level. Conversely the animals kept on lisinopril and amlodipine did not show any significant change in CK and GOT levels at the end of dosing period.

Animals kept on GlLAt combination did not revealed any significant change in CK

and GOT level at the end of dosing. On the contrary animals kept on GLoAt combination revealed highly significant increase in CK and GOT i.e. 314.54±4.23 µ/l and 137.96±2.10 µ/l with respect to control i.e. 205.35±6.98 µ/l and 42.80±0.75 µ/l respectively.

Animals received MAAt combination revealed significant increase in CK i.e. 284.92±0.97 µ/l with respect to control i.e. 205.35±6.98 µ/l. On the contrary there was no significant change in GOT level at the end of dosing.

Cardiac Tissue Examination

Gross examination of heart did not reveal any macroscopic changes in any group, while microscopic examination of cardiac tissue in all groups except GLoAt group did not revealed any microscopic changes (plate 1). However, animals received GLoAt combination showed elevation in dimension of heart from 3x2x1.2 cm to 3.5x2.5x1.5 cm as compared to control animals and other animal groups.

DISCUSSION & CONCLUSION

CK and GOT are the sign of cardiac pathology and elevated levels of these enzymes indicate muscular damage in cardiac tissue. In present study no histological changes in cardiac tissue were observed in animals of any groups.

However animals received metformin alone showed significant increase in GOT level. Studies show that although metformin is a safe drug for heart at usual doses but it may induce cardiac pathology. Metformin may attenuate nitric oxide which plays a key role in vascular supply to the body organ[13].

The animals received acarbose and glibenclamide alone showed highly significant increase in CK level where as animals received losartan and atorvastatin showed significant increase in CK with no change in GOT[14]. Since the increase in CK is not supported with microscopic examination of the cardiac tissue therefore it may be concluded that elevation of CK may be due to muscle injury since CK is widely distributed throughout the body[15].

The group of animals received GLoAt in combination showed highly significant increase in CK and GOT along with slight elevation in dimension of heart as compare to control. Although individual drugs in the combination did not show any change however, the elevation of dimension may be due to one of the side effect of losartan which has been used in this combination. This effect is not seen in any other group[16]. The animals with combination MAAt also showed a significant increase in CK which can be linked to the attenuation of nitric oxide due to metformin [17].

Hence from the results of present study it may be concluded that the GlLAt (Acarbose, Lisinopril and Atorvastatin) combination is safer than MAAt and GLoAt combinations, since no significant changes were observed in the level of cardiac enzymes and histology of cardiac tissue by this combination.

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Table 1. Drugs Induced Cardiac Toxicity[6]

Name of Drug	Possible Cardiac Toxicity
Ergotamine, fenfluramine, dexfenfluramine	Valvular disorders
Adenosine, Amphetamines, Beta-blockers (withdrawal), Beta-agonists, Caffeine, Dipyridamole, Ergotamine, Fluorouracil, Nifedipine (short acting), Theophylline, Thyroxin, Verapamil, Vincristine, Vinblastine	Myocardial ischemia
Amsacrine, Cisplatin, Cyclophosphamide Doxorubicin, Epirubicin, Fluorouracil, Idarubicin, Mitozantrone, Paclitaxel	Cardiomyopathy, contractile function
Corticosteroids, Erythropoietin, Interferon alfa, Ketoconazole, Moclobemide, Naloxone, NSAIDs, Estrogens, Sympathomimetics	Hypertension
Antacids (high sodium content), Anthracycline cytotoxic drugs, Antiarrhythmic drugs: Beta-blockers, Diltiazem Nifedipine, Verapamil; NSAIDs	Cardiac failure
Beta-blockers , Carbamazepine, Clonidine, Digoxin, Diltiazem, H_2-antagonists , Paclitaxel, Verapamil	Bradycardia
Antiarrhythmic drugs: Amiodarone, sotalol, quinidine, disopyramide; Antihistamines: Terfenadine, astemizole; Anti-infectives: Erythromycin, chloroquine, pentamidine; Psychiatric drugs, Tricyclic antidepressants, haloperidol, chlorpromazine, sertindole, lithium, thioridazine, pimozide,	QT interval prolongation
Digoxin, verapamil or a beta-blocker	Atrial Fibrillation

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Table 2. Comparison of Cardiac Enzymes Following 60 Days Administration of Drugs & Their Combinations

Cardiac Enzymes/ Groups	CK (µ/l)	GOT (µ/l)
Control	205.35±6.98	42.80±0.75
Acarbose	412.2±2.59**	46.00±2.41
Glibenclamide	308.9±3.54**	36.80±2.01
Metformin	241.62±1.76	84.48±4.89*
Lisinopril	253.12±0.98	42.12±1.76
Losartan	112.06±0.59**	44.86±0.94
Atorvastatin	172.92±6.12*	54.04±0.87
Amlodipine	183.28±2.32	46.65±1.51
GlLAt	196.41±6.51	45.12±1.40
GLoAt	314.54±4.23**	137.96±2.10**
MAAt	284.92±0.97*	37.6±0.15

Abbreviations:
GlLAt: Acarbose, Lisinopril and Atorvastatin,
GLoAt: Glibenclamide, Losartan and Atorvastatin and
MAAt: Metformin, Amlodipine and Atorvastatin.
n=10
Mean ± S.E.M
*p < 0.05 significant with respect to control
**p <0.005 highly significant with respect to control

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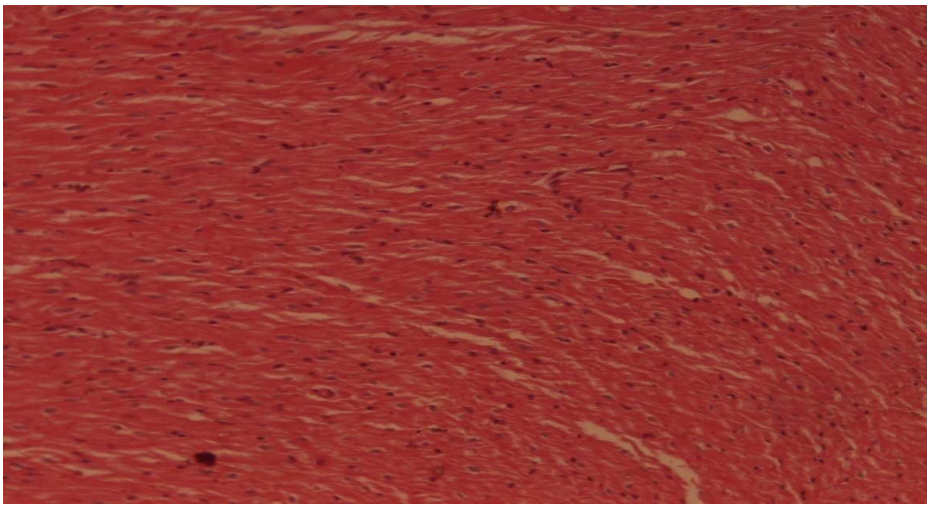

Figure.1. Cardiac Tissue Showing no Change