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Pharmacokinetic Drug - Drug Interactions between Concomitantly Used Metformin with Pravastatin

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ABSTRACT

The present study is aimed to investigate the safety and reliability of anti diabetic drug Metformin and possible drug interaction with Pravastatin when they were administered as combination treatment. The study was conducted on healthy Wistar and streptozotocin induced diabetic rats. A simple and sensitive high performance liquid chromatographic method was developed for the simultaneous estimation of Metformin and Pravastatin in rat plasma and also to estimate possible pharmacokinetic parameters of these drugs after oral administration. There was no significant difference in the t_{max} of Metformin alone and combination with Pravastatin on day 1 and day 8 respectively. These were no significant increase in both AUC $_{(0 - 24\ h)}$ and AUC $_{(0 - \alpha)}$ of Metformin alone and combination of Pravastatin on day 1 and day 8 respectively. Similarly there was no significant enhancement in the C_{max} between Metformin alone and combination with Pravastatin on day 1 and day 8 respectively. There is however no significant difference in C_{max}, t½, values. Similarly there was no significant difference in the t_{max} of Pravastatin alone and combination with Metformin on day 1 and day 8 respectively and no significant enhancement in C_{max}, t_{max}, t1/2, values between Pravastatin alone and combination with Metformin on day 1 and day 8 respectively. In the present study, based on the results it can be concluded that the concurrent administration of these two drugs have potential benefit in the treatment of Diabetes and hyperlipidemia. In addition, due to their insignificant pharmacokinetic interaction the combinational therapy can be safe and highly advantageous in hyperlipidemia patients with diabetes.

Keywords: Metformin, Pravastatin, hyperlipidemia, Diabetes mellitus.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by a hyperglycemia caused by insulin deficiency, often combined with insulin resistance. In diabetes, the homeostasis of carbohydrate and lipid metabolism is improperly regulated by the pancreatic

hormone, insulin; resulting in an increased blood glucose level. [1] Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. Diabetes mellitus is classified on the basis of the pathogenic process that leads to the hyperglycemia. The broad categories of DM are designated type 1 and type 2. [2] Metformin lowers blood glucose concentration and improves insulin sensitivity by reducing hepatic gluconeogenesis and enhancing insulin-simulated peripheral glucose uptake. It also inhibits adipose tissue lipolysis, thereby reducing circulating levels of free fatty acids (FFA). [3] Metformin, an oral anti-diabetic drug, is being considered increasingly for treatment and prevention of cancer, obesity as well as for the extension of healthy life span. [4] Metformin is not metabolized at all but is completely excreted in urine. Metformin may therefore accumulate and cause lactic acidosis if other medications have induced renal failure. [5] When patients are diagnosed with diabetes, a large number of medications become appropriate therapy. These include medications for dyslipidemia, hypertension, anti-platelet therapy, and glycemic control which may lead to drug interactions with antidiabetic drugs. [6] Metformin has many drug-disease interactions that can increase the risk of metformin-associated lactic acidosis (MALA). [6] Drug interactions are often categorized as pharmacodynamic or pharmacokinetic in nature. [6] A pharmacodynamic drug interaction is related to the drug's effect on the body. Pharmacodynamic drug interactions can be either beneficial or detrimental to patients. [6] Any drug that has the potential to raise blood glucose may produce apparent inefficacy of an oral hypoglycaemic drug. Stopping a drug which causes hyperglycaemia may produce a significant fall in blood glucose. This may require a parallel reduction in the dose of a hypoglycemic drug. [5] Some drugs can lower blood glucose, but the mechanisms of action are not well understood. Taking one of these drugs with a hypoglycemic drug might cause clinically significant hypoglycaemia. The patient may need a lower dose or even have to cease the oral hypoglycemic drug. Conversely stopping a drug with the potential to lower blood glucose might produce relative inefficacy of a hypoglycemic drug and create a need for an increased dose. [5]

MATERIALS AND METHODS

Materials

Drugs and chemicals

Metformin and Pravastatin were procured from aurobindo laboratories as a gift sample. All HPLC grade solvents (methanol and water) were procured from finar chemicals Ltd., Ahmadabad. All chemicals used were analytical grade.

Animal study

Male Wistar rats (weighing 200-220 g) were procured from the animal house CMR College of Pharmacy, Hyderabad. Animals were randomly divided into four groups each group contains six animals. Each rat was maintained under controlled lab environment atmosphere humidity of 50%, fed with standard pellet diet and water *ad libitum*. The protocol of animal study was approved by the institutional animal ethical committee with No. **IAEC/1292/VCP/Y6/Ph D-16/61**.

Study Design [7]

The rats were grouped as follows

Group I: Metformin alone in single dose/day in diabetic rats.

Group II: Pravastatin alone in single dose/day in diabetic rats.

Group III: Pravastatin alone in single dose/day in normal healthy rats

Group IV: Metformin and Pravastatin concomitant administration as a single dose/day in diabetic rats.

Collection of Blood Samples

After administration of the drugs, blood samples of 0.5 ml were drawn from each anesthetized (isoflurane) rat at pre-determined time intervals was collected from the retro-orbital plexus using a capillary tube into pre-labelled eppendorf tubes containing 10% of K_2EDTA anticoagulant (20µL). The time intervals for the sample collection were 0 (Pre dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 18 and 24 hours (post dose), Equal amount of saline was administered to replace blood volume at every blood withdrawal time.

Plasma was obtained by centrifuging blood samples by using cooling centrifuge (REMI ULTRA) at 3000 rpm for 5 minutes. The obtained plasma samples were transferred into pre-labelled micro centrifuge tubes and stored at −30°C until bio analysis of pharmacokinetic and pharmacodynamic parameters. As described above, all the procedures were followed on day 8 also. Pharmacokinetic parameters were calculated by non-compartmental analysis by using Win Nonlin® 5.1 software. Concentrations obtained from the above bio-analytical method were compiled.

Method of Analysis

Preparation of Plasma Samples for HPLC Analysis

Rat plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of Acetonitrile by vortexing for 1 min. After centrifugation (5000–6000 rpm for 10 min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200µ1 of mobile phase was injected for HPLC analysis.

For HPLC an Inertsil ODS 3V, 250 × 4.6 mm, C18 column with 5µm particle size and the mobile phase consisting of A mixture of Phosphate buffer and Methanol in the ratio of 60:40 v/v, the flow rate was maintained at 1ml/min and the eluent was monitored at 215 nm. Phenformin used as internal standard. The

retention times of Metformin, Pravastatin and Phenformin were found to be 7.2, 4.6 and 3.2 min respectively.

Standard calibration curve of Metformin and Pravastatin in rat plasma

Different concentration (0.05, 0.1, 0.5, 1, 5, 10, 20, 40 ng/ml) of Metformin, Pravastatin in plasma were prepared for calibration curve. The samples were treated as above for protein precipitation method and peak areas of Metformin and Pravastatin were noted down. The peak area ratios obtained at different concentrations of the Metformin, Pravastatin were plotted using UV – Vis detector at 220 nm.

Pharmacokinetic Analysis

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24 hours, which was determined by linear trapezoidal rule and $AUC_{0-\alpha}$ refers to the AUC from time at zero hours to infinity.

The $AUC_{0-\alpha}$ was calculated using the formula AUC_{0-t} + $[C_{last}/K]$ where C_{last} is the concentration in µg/ml at the last time point and K is the elimination rate constant. Various pharmacokinetic parameters like area under the curve [AUC], elimination half life [t½]. Volume of distribution (V/f) total clearance (Cl/f) and mean residence time for each subject using a non-compartmental analysis by using Win Nonlin® 5.1 software.

Statistical Analysis

Statistical comparisons for the pharmacokinetic – Pharmacodynamic study among, Metformin, Pravastatin alone and in combination groups and plasma concentration – response study among concentrations and time were carried out with student's paired T-Test a value of $P<0.05$ was considered to be statistically significant. Data were reported as mean ± S.E.M linear regressions were used to determine the relationship between total plasma concentrations and pharmacokinetic and pharmacodynamic parameters. The mean concentration versus time profile of Metformin and Pravastatin in rat plasma is shown in Figures 1, 2, 3, 4, 5 and 6.

RESULTS AND DISCUSSION

In the present study, Metformin is completely absorbed after oral administration with peak plasma concentration of 24.34 ± 0.3µg/ml after 2 hours of dosing on day 1. In combination with Metformin and Pravastatin on day 1, the peak plasma concentration of Metformin 26.03 ± 0.12µg/ml occurred 2 hours after dosing. There was no significant increase in peak plasma concentration levels. Similarly Pravastatin is completely absorbed after oral administration with peak plasma concentration 3.02 ± 0.03µg/ml occurred 2 hour after dosing on day 1 in combination with Metformin and Pravastatin on day 1.

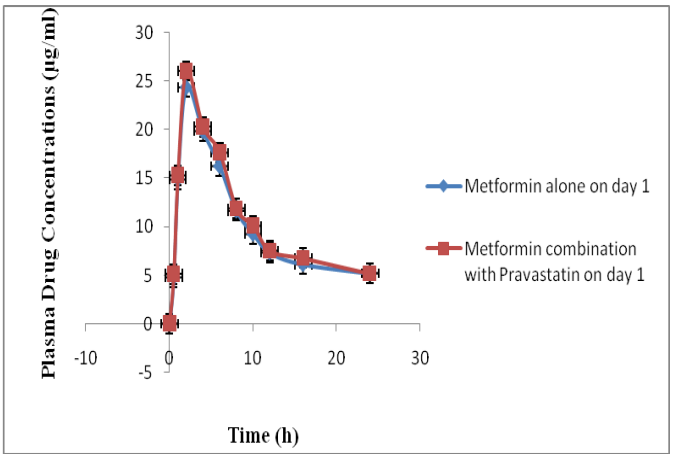

Fig. 1: Mean ± S.E.M, plasma levels (µg/ml) of Metformin alone and in Combination with Pravastatin on day 1

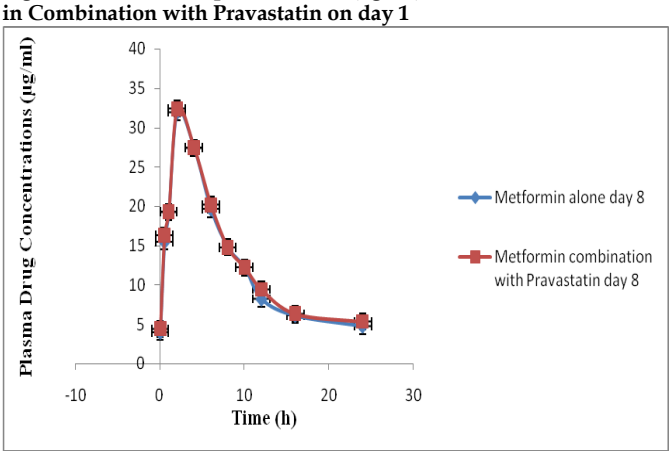

Fig. 2: Mean ± S.E.M, plasma levels (µg/ml) of Metformin alone and in Combination with Pravastatin on day 8

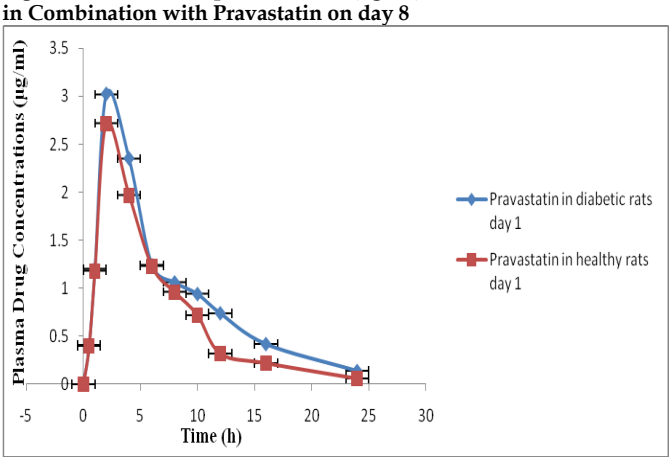

Fig. 3: Mean ± S.E.M, plasma levels (µg/ml) of Pravastatin in diabetic versus healthy male Wistar rats on day 1

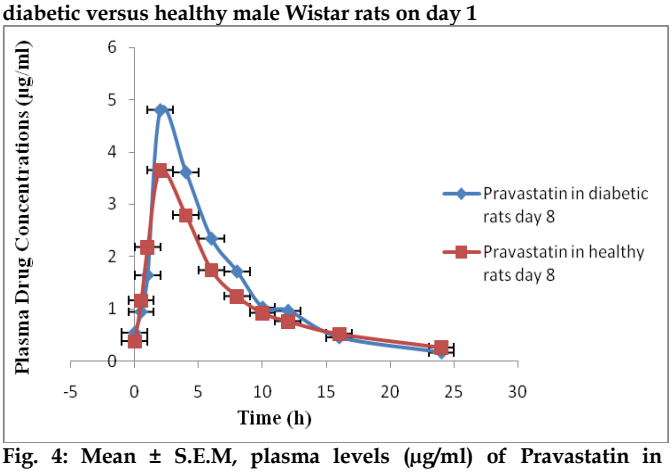

Fig. 4: Mean ± S.E.M, plasma levels (µg/ml) of Pravastatin in diabetic versus healthy male Wistar rats on day 8

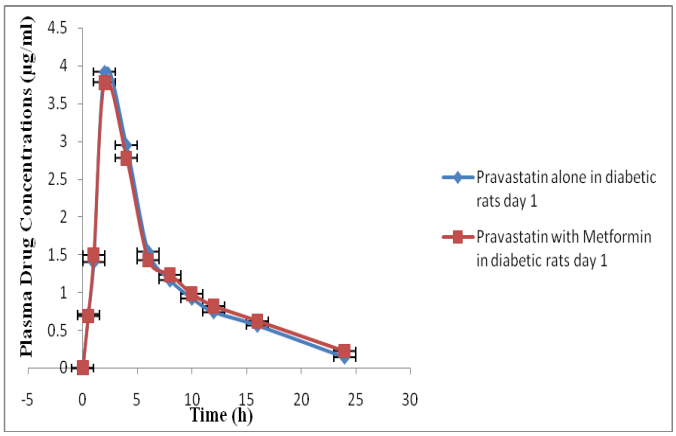

Fig. 5: Mean ± S.E.M, plasma levels (µg/ml) of Pravastatin alone and in Combination with Metformin on day 1

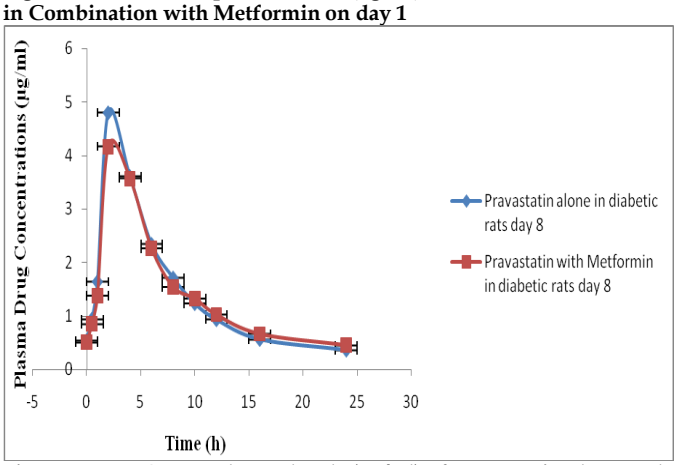

Fig. 6: Mean ± S.E.M, plasma levels (µg/ml) of Pravastatin alone and in Combination with Metformin on day 8

The peak plasma concentration of Pravastatin 4.80 ± 0.04µg/ml occurred 2 hours after dosing. There was no significant increase in the peak plasma concentration levels similarly on day 8 of Metformin alone and with combination of Metformin with Pravastatin on day 8. Peak plasma concentration are 31.92 ± 0.22µg/ml and 32.41 ± 0.10 S µg/ml respectively similarly Pravastatin on day 8 and combination with Metformin concentrations are 4.80 ± 0.04µg/ml and 4.615 ± 0.04µg/ml respectively. There was no significant difference in peak plasma concentration on day 8 (P>0.05). There was no significant differences were observed between diabetic and healthy Pravastatin treated rats on day 1 and day 8 respectively (P<0.05) on oral administration of Pravastatin alone and with combination of Metformin. With Pravastatin on day 1 showed a 2% increase in the AUC_{0-24} of Metformin compared to combinational treatment similarly. Pravastatin on day 1 and with combination Metformin with Pravastatin on day 1 administration resulted in an increase in the AUC_{0-24} of Pravastatin compared with combinational treatment. Similarly on day 8 of Metformin and Pravastatin in combination treatment were 1.65% and 2.8% increase in the AUC_{0-24} respectively. The mean AUC_{0-24} of Pravastatin in diabetic (HL) rats was 33.49 ± 0.20µg/ml /h and 44.11 ± 0.22µg/ml/h which was reduced to 21.9 ± 0.11µg/ml/h and 38.22 ± 0.09 µg/ml/h Pravastatin in healthy rats on day 1 and day 8 treatment (P<0.05) respectively.

Table 1: Mean ± S.E.M, pharmacokinetic parameters of Metformin alone and in Combination with Pravastatin on day 1

Parameters	Metformin alone	Metformin combination with Pravastatin
C_{max}	25.74 ± 0.39	26.03 ± 0.12
t_{max}	2 ± 0	2 ± 0
AUC_{o-t} (µg/ml/h)	272.45 ± 0.74	276.37 ± 0.52
AUC_{o-inf} (µg/ml/h)	368.82 ± 2.50	356.15 ± 1.85
$T_{1/2}$ (h)	6.56 ± 0.28	6.64 ± 0.09

Table 2: Mean ± S.E.M, pharmacokinetic parameters of Metformin alone and in Combination with Pravastatin on day 8

Parameters	Metformin alone	Metformin combination with Pravastatin
C_{max}	31.92 ± 0.22	32.41 ± 0.1
t_{max}	2 ± 0	2 ± 0
AUC_{o-t} (µg/ml/h)	337.36 ± 0.38	343.38 ± 0.49
AUC_{o-inf} (µg/ml/h)	396.36 ± 0.63	413.49 ± 0.74
$T_{1/2}$ (h)	6.496 ± 0.024	6.08 ± 0.018

Table 3: Mean ± S.E.M, pharmacokinetic parameters of Pravastatin in diabetic versus healthy male Wistar rats on day 1

Parameters	Pravastatin in diabetic rats	Pravastatin in healthy rats
C_{max}	3.92 ± 0.03	2.72 ± 0.03
t_{max}	2 ± 0	2 ± 0
AUC_{o-t} (µg/ml/h)	33.49 ± 0.20	21.9 ± 0.118
AUC_{o-inf} (µg/ml/h)	52.23 ± 1.36	27.49 ± 0.808
$T_{1/2}$ (h)	5.22 ± 0.49	5.03 ± 1.11

Table 4: Mean ± S.E.M, pharmacokinetic parameters of Pravastatin in diabetic versus healthy male Wistar rats on day 8

Parameters	Pravastatin in diabetic rats	Pravastatin in non diabetic rats
C_{max}	4.80 ± 0.04	3.65 ± 0.06
t_{max}	2 ± 0	2 ± 0
AUC_{o-t} (µg/ml/h)	44.11 ± 0.225	38.22 ± 0.09
AUC_{o-inf} (µg/ml/h)	61.57 ± 0.43	67.37 ± 0.336
$T_{1/2}$ (h)	5.49 ± 0.186	5.92 ± 0.0908

Table 5: Mean ± S.E.M, pharmacokinetic parameters of Pravastatin alone and in Combination with Metformin in diabetic rats on day 1

Parameters	Pravastatin alone	Pravastatin with Metformin
C_{max}	3.92 ± 0.03	3.783 ± 0.02
t_{max}	2 ± 0	2 ± 0
AUC_{o-t} (µg/ml/h)	33.49 ± 0.016	31.62 ± 0.20
AUC_{o-inf} (µg/ml/h)	52.33 ± 1.37	42.16 ± 0.52
$T_{1/2}$ (h)	5.22 ± 0.49	5.57 ± 0.27

Table 6: Mean ± S.E.M, pharmacokinetic parameters of Pravastatin alone and in Combination with Metformin in Diabetic rats on day 8

Parameters	Pravastatin alone	Pravastatin with Metformin
C_{max}	4.80 ± 0.04	4.615.± 0.04
t_{max}	2 ± 0	2 ± 0
AUC_{o-t} (µg/ml/h)	33.5 ± 0.2253	41.6 ± 0.25
AUC_{o-inf} (µg/ml/h)	52.6 ± 0.43	59.76 ± 0.88
$T_{1/2}$ (h)	15.23 ± 0.18	12.89 ± 0.29

The half life was similar with alone and combination treatment on day 1 and day 8. All these changes were not statistically significant (P>0.05). All the results were showed in Table 1-6.

In the present study, based on the results obtained from kinetic study it is evident that the single dose of

Metformin, Pravastatin individually and concomitantly treated diabetic rats did not show any bio statistically significant interactions in its pharmacokinetic parameters.

So, it can be concluded that the concurrent administration of these two drugs have potential benefit in the management of diabetic patients with hyperlipidemia. In addition, due to their insignificant pharmacokinetic interaction the combinational therapy can be safe and highly advantageous in patients with diabetes and constipation.

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