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EFFECT OF EMTRICITABINE ON PHARMACOKINETICS OF SITAGLIPTIN IN DIABETIC RABBITS

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Abstract

The availability of potent combination antiretroviral regimens has resulted in a dramatic reduction in HIV-1 associated morbidity and mortality in the developed world. However, HIV infection and treatment has been associated with the development of insulin resistance, glucose intolerance and diabetes. The aim of the present study was to evaluate the effect of emtricitabine (anti-HIV drug) on pharmacokinetics of sitagliptin (antidiabetic drug) in diabetic rabbits.

Alloxan-induced diabetic model in rabbits has been used in this study. After the induction of diabetes, sitagliptin (7 mg/kg/po) and emtricitabine (14 mg/kg/po) for 7 days. The pharmacokinetic parameters like $t_{1/2}$, AUC, Clearance, Tmax and C max of sitagliptin with and without combination of emtricitabine treatment were determined. The plasma concentration-time profiles of sitagliptin following single dose and multiple dose treatment of emtricitabine were found to be similar. There was no change in the pharmacokinetic parameters in presence of emtricitabine indicates the no significant (p>0.05) interaction.

Keywords: Sitagliptin, Emtricitabine, Pharmacokinetics and Diabetic rabbits.

1. Introduction

Polypharmacy is very common practice for the patients suffering with chronic diseases such as diabetes mellitus and HIV infection, and thus leads to undesirable potent drug-drug interactions (pharmacodynamic and/or pharmacokinetic) which can alter the safety and efficacy profile of a drug in many ways. Recent reports [1, 2] reveals that drug interactions played a vital role in reported adverse events and that majority of the drugs withdrawn for safety reasons from the US market were related with significant drug-drug interactions. The importance of this fact is further emphasized by increased post marketing adverse event reports by 240% over the last decade[3].There is a propensity for drug-drug

interactions in patients with concurrent type 2 diabetes mellitus and HIV infection that are likely to be treated with antiretroviral and antidiabetic therapy. Diabetes mellitus is a metabolic disorder that needs treatment for prolonged periods and maintenance of normal blood glucose level is very important in this condition, since both hyperglycemia as well as hypoglycemia is unwanted phenomenon [4, 5]. Many studies suggested that PI therapy [6, 7] is linked to the development of diabetic complications; it is of importance to propose therapeutic strategies with fewer side effects, such as the use of the nucleoside reverse transcriptase inhibitors. In this contest, there are more chances of co-administration of the nucleoside reverse transcriptase inhibitors with antidiabetic drugs in patients with concurrent type-2 diabetes mellitus and HIV infection which may leads to potent drug-drug interactions. However, there is no much information available to elucidate the mechanisms of drug interactions between NRTIs and antidiabetic drugs which are essential to the clinicians to prescribe the rational drug combinations with respect to safety and efficacy. Sitagliptin is a dipeptidyl-peptidase inhibitor (DPP-4 inhibitor) has been shown to be effective, well tolerated, and safe in the treatment of type 2 diabetes in monotherapy or in the combination with metformin or thiazolidinediones. It reduces the glycemic parameters HbA1c and fasting and postprandial glucose and improves beta-cell function[8]. Emtricitabine is a potent nucleoside analog with a convenient once-daily dosing schedule approved for the treatment of HIV infection[9]. The present study was conducted on diabetic rabbits to assess the effect of emtricitabine on the pharmacokinetics of sitagliptin.

2. Materials and Methods

2.1 Drugs and Chemicals

Sitagliptin and Emtricitabine are the gift samples from (Mylan Laboratories, Hyderabad) and (Aurobindo Pharmaceuticals Ltd, Hyderabad) respectively. Methanol and water used were of HPLC grade while triethanolamine AR grade.

2.2 Animals

Normal rabbits of either sex of 3 months of age weighing between 1.5-2.0 kg were procured from Mahaveer enterprises. Rabbits were fed with a commercial pellet diet (Rayan's Biotechnologies Pvt Ltd., Hyderabad, India) and water ad libitum. The animals were maintained under standard laboratory conditions. All the animal's experiments were carried out as per the guidelines of the committee for the purpose of control and supervision of experiments on animals, ministry of environment and forest, Government of India. In rabbits, diabetes mellitus was induced by a single

intravenous injection of alloxan monohydrate (150 mg/kg, body weight), dissolved in 0.1 M sodium citrate buffer pH 4.5. In order to reduce death due to hypoglycemic shock, alloxan-treated rabbits received 5% of glucose instead of water for 24 h after diabetes induction[10]. Samples were collected from marginal ear vein and analyzed for glucose levels. Rabbits which have shown more than 200 mg/dl blood glucose levels were used for further studies. Emtricitabine was suspended in sodium CMC for oral administration[11]. Sitagliptin solution was prepared by dissolving it in 5% gum acacia. These drugs were administered by oral route.

2.3 Non-compartmental pharmacokinetic analysis

Pharmacokinetic parameters were determined on subjecting the drug concentration-time data to non-compartmental analysis using Win Nonlin (Version 5.2.1) software.

2.4 Statistical Analysis

All the experimental values are expressed as mean $\pm$ SD. The PK parameters were compared with sitagliptin control value at each time point using One-Way ANOVA followed by Tukey's multiple comparison test. The statistical significance was judged at the 0.05 probability level. Pharmacokinetic analysis was carried by non compartmental method using Win Nonlin software.

2.5 Experimental Design

A group of five rabbits were employed in the study. The study was planned and designed in three groups.

Group –I: Diabetic rabbits treated with sitagliptin (7 mg/kg/po)

Group-II: Diabetic rabbits treated with emtricitabine (14 mg/kg/po) and sitagliptin

(7 mg/kg/po)

Group-III: Diabetic rabbits treated with emtricitabine (14 mg/kg/po) for 7 days and on 8th day they receive sitagliptin (7 mg/kg/po).

The same group of rabbits was repeated with a washout period of one week after every treatment. Blood samples were collected from each animal at time intervals of 0.0, 1.0, 2.0, 3.0, 4.0, 8.0, 16.0 and 24.0 hours. The time points for the pharmacokinetic study were carefully selected to get a comprehensive picture of the pharmacokinetics of test product in rabbits. Plasma was separated after centrifugation for 15 minutes at 4000 rpm. Sitagliptin concentration levels were measured by using validated HPLC method[12].

3. Results & Discussion

Effect of Emtricitabine on Pharmacokinetics of Sitagliptin

The effect of emtricitabine on pharmacokinetics of sitagliptin was studied with single dose and multiple dose treatment. The blood samples were collected at different time intervals were analyzed for sitagliptin concentration and the results of estimated pharmacokinetic parameters are represented in Table 1.2 .The mean plasma concentration profile of sitagliptin is represented in Table 1.1 and Figure 1.

The plasma concentration –time profiles of sitagliptin following single dose and multiple dose treatment of emtricitabine were found to be similar. The mean Cmax was found to be 3.98 ± 1.06, 3.38 ± 0.38 and 3.78 ± 0.58 µg/ml and the Tmax was found to be 3.0, 3.16 and 3.0 hr for sitagliptin and with combination of single dose and multiple doses of emtricitabine respectively. This shows that the rate and extent of absorption were found be comparable between the sitagliptin alone and in combination with emtricitabine. The mean $AUC_{0-\infty}$ was found to be 14.18 ± 3.35, 15.12 ± 4.50 and 14.03 ± 4.62 µg.hr/ml, mean half-life was found to be 3.41 ± 1.20, 4.04 ± 1.33 and 3.51 ± 0.90 hr and mean clearance was found be 1.50 ± 0.29, 1.72 ± 1.34, 1.65 ± 0.82 L/hr in sitagliptin alone and in combination with single dose and multiple doses of emtricitabine respectively and no statistically significant difference was observed at ($P>0.05$).

Table-1.1: Plasma concentration levels of Sitagliptin alone and in combination with single dose and multiple dose treatment of Emtricitabine in diabetic rabbits.

Time (hr)	Sitagliptin (µg/ml)	Emtricitabine + Sitagliptin (SDT) (µg/ml)	Emtricitabine+ Sitagliptin(MDT) (µg/ml)
0	0.000	0.000	0.000
1	0.713 ± 1.875	0.661 ± 0.115	0.674 ± 0.058
2	2.336 ± 0.724	1.996 ± 0.583	1.857 ± 1.045
3	3.432 ± 0.290	3.159 ± 0.619	2.915 ± 1.336
4	1.183 ± 0.206	1.486 ± 1.027	1.290 ± 1.395
8	0.584 ± 0.041	0.536 ± 0.164	0.664 ± 0.404
16	0.105 ± 0.027	0.247 ± 0.153	0.141 ± 0.046
24	0.034 ± 0.000	0.031 ± 0.037	0.024 ± 0.024

SDT, Single dose treatment; MDT, Multiple dose treatment

Figure-1:

Mean concentraion levels of Sitagliptin alone and in combination with single dose and multiple dose treatment of Emtricitabine in diabetic rabbits
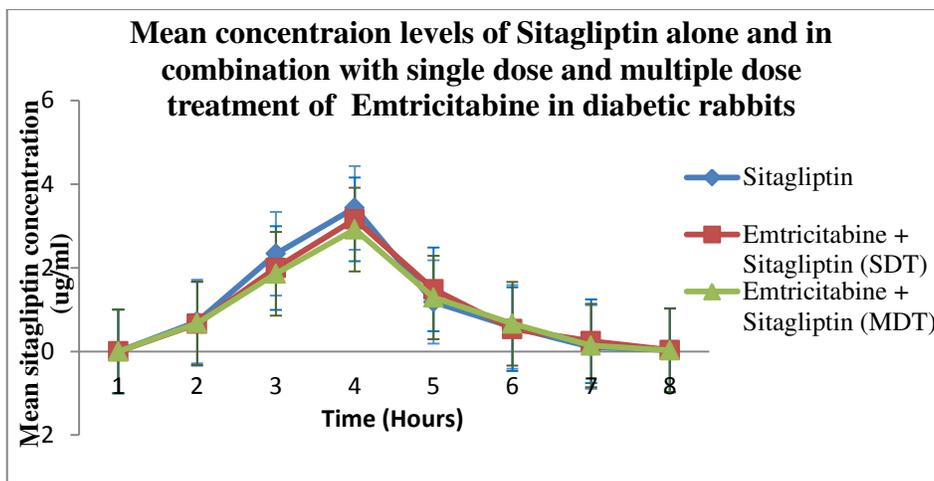
Table-1.2: Pharmacokinetic parameters (Mean $\pm$ SD) of Sitagliptin in presence and absence of Emtricitabine in diabetic rabbits.

PK parameters	Sitagliptin	Emtricitabine + Sitagliptin (SDT)	Emtricitabine + Sitagliptin (MDT)
Tmax(hr)	3.0 $\pm$ 0.63	3.16 $\pm$ 0.41	3.0 $\pm$ 0.63
Cmax (ug/ml)	3.98 $\pm$ 1.06	3.38 $\pm$ 0.38	3.78 $\pm$ 0.58
AUC_{0-t} (ug.hr/ml)	13.87 $\pm$ 2.91	14.78 $\pm$ 4.45	13.88 $\pm$ 4.67
$AUC_{0-\infty}$(ug.hr/ml)	14.18 $\pm$ 3.35	15.12 $\pm$ 4.50	14.03 $\pm$ 4.62
$AUMC_{0-t}$	71.49 $\pm$ 29.95	88.19 $\pm$ 36.87	78.28 $\pm$ 30.96
$AUMC_{0-\infty}$	80.83 $\pm$ 45.02	97.99 $\pm$ 40.58	82.78 $\pm$ 29.86
MRT hr	5.02 $\pm$ 1.07	5.75 $\pm$ 1.05	5.57 $\pm$ 0.42
K_{el} hr^{-1}	0.23 $\pm$ 0.07	0.19 $\pm$ 0.07	0.21 $\pm$ 0.06
$t_{1/2}$ hr	3.41 $\pm$ 1.20	4.04 $\pm$ 1.33	3.51 $\pm$ 0.90
Vd L/kg	6.28 $\pm$ 1.47	6.84 $\pm$ 2.67	7.21 $\pm$ 1.56
Cl L/hr	1.50 $\pm$ 0.29	1.72 $\pm$ 1.34	1.65 $\pm$ 0.82

SDT, Single dose treatment; MDT, Multiple dose treatment.

Discussion:

The pharmacokinetic data clearly indicate that emtricitabine had not altered the onset of action (Tmax), the overall plasma exposure (AUC), peak concentration (Cmax) of sitagliptin and $t_{1/2}$ indicating no significant pharmacokinetic interaction. The plasma concentration of sitagliptin in the groups of sitagliptin alone and in combination with emtricitabine were found to be similar and no statistically significant difference was observed at (P>0.05). Therefore, these experimental findings explicitly convince that there is no significant pharmacokinetic interaction between

emtricitabine and sitagliptin. The pharmacodynamic observations are in agreement with our pharmacokinetic findings. Maximum plasma concentration was achieved at 3 hr representing the consistency between pharmacodynamic and pharmacokinetic results.

The results indicated the absence of pharmacodynamic and pharmacokinetic interaction between sitagliptin and emtricitabine in diabetic rabbits.

4. Conclusion:

The present study results suggest that the pharmacokinetic interaction was not observed after single and multiple dose treatment with emtricitabine and sitagliptin. On pharmacokinetic interaction of sitagliptin with emtricitabine has shown similar effect on bioavailability of sitagliptin as a single drug. In conclusion, the results of the present study showed that the combination of sitagliptin and emtricitabine is considered to be safe for clinical benefit.

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