Research Article

Studies on Pharmacodynamic Drug Interactions Between Sitagliptin and Emtricitabine in Normal and Diabetic Rats

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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 emergence of these glucose disturbances and diabetic conditions presents a pharmacological Challenge because of the possible pharmaco-dynamic interactions associated with ant diabetic drugs and antiretroviral drugs. The present study was carried in Wistar albino rats (normal and diabetic) to evaluate the influence of emtricitabine on sitagliptin. The blood samples were collected at different intervals and blood glucose levels were measured by GOD-POD method. In the present study, sitagliptin had not produced any significant reduction in blood glucose levels alone or in combination with single dose or multiple dose treatment of emtricitabine in normal and diabetic rats. This confirms the absence of pharmaco-dynamic interaction in normal and diabetic rats with the combination of emtricitabine and sitagliptin.

Keywords: Drug interaction, Emtricitabine, Sitagliptin.

INTRODUCTION

The study of mechanisms of drug interactions is of much value in selecting the drug concentrations to provide rational therapy. The drug interaction studies assume much importance especially for drugs that have narrow margin of safety and where the drugs are used for prolonged period of time. Diabetes mellitus is a metabolic disorder which needs prolonged periods of treatment and maintenance of normal blood glucose level is very important in this condition, since both hyperglycemia and hypoglycemia is unwanted phenomenon[1].

Diabetes mellitus is a chronic disorder characterized by elevated blood glucose levels and disturbances in fat, carbohydrate and protein metabolism and with increased risk of complications from vascular disease[2]. Type-1 diabetes is caused due to decrease in the synthesis of insulin and type-2 diabetes is characterized by hyperglycemia in the context of insulin resistance and relative insulin deficiency. There are 143 million people worldwide sufferings from diabetes[3] and the number may probably double by the year 2030[4]. The prevalence rate of diabetes in India is estimated to be 1-5%. Among the many metabolic perturbations that occur as a result of Human Immuno deficiency Virus (HIV) infection and its treatment may cause alterations in normal blood glucose homeostasis and remain as a particularly prevalent and alarming clinical change in affected patients[5]. Much of concern is due to the recognition of the long-term complications of insulin resistance and hyperglycemia and understood the risk of the growing worldwide epidemic of type-2 diabetes mellitus[6]. Insulin resistance, impaired glucose tolerance and type-2 diabetes are conditions that are increasingly described in HIV-1 infected subjects receiving highly active antiretroviral therapy (HAART). HAART generally includes nucleoside reverse transcriptase inhibitors and protease inhibitors. Many studies have observed that PI therapy[7] is linked with the development of metabolic complications; it is of important to propose therapeutic strategies with fewer side effects, such as the use of the non-nuleoside reverse transcriptase inhibitors (NNRTIs) and this approach successfully control HIV infection[8].

Oral hypoglycemic agents are used in the treatment of type-2 diabetes, among which sitagliptin is preferred in therapy. Sitagliptin is a selective, reversible inhibitor of dipeptidyl-peptidase 4 approved by the Food and Drug Administration for the treatment of type-2 diabetes[9,10]. Emtricitabine is a synthetic nucleoside analog with activity against human immunodeficiency virus type-1 (HIV-1) reverse transcriptase. Since there is every possibility for the combined use of sitagliptin and emtricitabine in chronic diabetics with associated HIV infection, the study is planned to investigate the effect of emtricitabine on blood glucose and their effect on the activity of sitagliptin in rats (normal and diabetic) and to evaluate the safety and effectiveness of the combination with respect to blood glucose level.

MATERIALS AND METHODS

Sitagliptin and emtricitabine were the gift samples from Mylan Labs (Hyderabad) and Aurobindo Pharma Ltd (Hyderabad, India) respectively. Alloxan monohydrate was purchased from LOBA Chemie (Mumbai, India). Glucose kits (Span diagnostics) were purchased from local

pharmacy. All other reagents/chemicals used were of analytical grade.

Albino Wistar rats of either sex, weight range 200-250 g. They were procured from Mahaveer enterprises, Hyderabad. All rats were kept for acclimatization for seven days prior to start the study. They were maintained under standard laboratory conditions at an ambient temperature of 25 ± 2 °C and 50 ± 15% relative humidity with a constant daily cycle of 12-h light/12-h dark cycle. Animals were fed with a commercial pellet diet (Rayan's Biotechnologies Pvt Ltd., Hyderabad, India) and water *ad libitum.* They were fasted for 18-h prior to the experiment and during the experiment they were withdrawn from food and water. The animal experiments were performed after prior approval of the study protocol by Institutional Animal Ethics Committee and by the government regulatory body for animal research. (Reg.No. 1722/Ro/Ere/S/13CPCSEA). The study was conducted in accordance with the guidelines provided by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Diabetes was induced in rats by the administration of alloxan monohydrate dose 140 mg/kg body weight intraperitoneally for two consecutive days[11]. After 72 hr, samples were collected from rats by retro orbital puncture of all surviving rats and serum was analysed for glucose levels. Rats with blood glucose levels of 200 mg/dl and above were considered as diabetic and selected for study.

Antiretroviral drugs were suspended in sodium CMC for oral administration[12]. Sitagliptin solution was prepared by dissolving it in 5% gum acacia.

Study design

The rats were fasted for 18 hr prior to the experiment with water ad libitum. Eight groups were employed in the study and each group comprised of six rats. The study is planned and designed in following way.

Group-I: Normal rats treated with sitagliptin (10 mg/kg/po)

Group-II: Normal rats treated with emtricitabine (3.6 mg/kg/po)

Group-III: Normal rats treated with emtricitabine (3.6 mg/kg/po) ans sitagliptin (10 mg/kg/po)

Group-IV: Normal rats treated with emtricitabine (3.6 mg/kg/po) for 7 days and on 8th day they received sitagliptin (10 mg/kg/po)

Group –V: Diabetic rats treated with sitagliptin (10 mg/kg/po)

Group- VI: Diabetic rats treated with emtricitabine (3.6 mg/kg/po)

Group- VII: Diabetic rats treated with emtricitabine (3.6 mg/kg/po) and sitagliptin (10 mg/kg/po)

Group-VIII: Diabetic rats treated with emtricitabine (3.6 mg/kg/po) for 7 days and on 8th day they received sitagliptin (10 mg/kg/po).

Blood samples were withdrawn from retroorbital plexus[13] of each animal at time intervals of 0.0, 1.0, 2.0, 3.0, 4.0, 8.0, 16.0 and 24.0 hours. These blood samples were analysed for blood glucose by GOD/POD method[14] using commercial glucose kits.

Data and statistical analysis

Data were expressed as mean ± SD. The significance was determined by Tukey's multiple comparison tests.

RESULTS

In the present study, sitagliptin had not produced any significant reduction in blood glucose levels alone or in combination with single dose or multiple dose treatment of emtricitabine in normal rats (Table 1 and in Figure 1).

In diabetic rats, sitagliptin alone and in combination with single and multiple dose treatment of emtricitabine produced significant antihyperglycemic activity. The percent reduction in blood glucose levels was found to be 49.58 %, 48.11 % and 49. 0 % at 3 h respectively (Table 2 and Figure 2). With combination of emtricitabine as single dose and multiple dose treatment emtricitabine had no significant impact on sitagliptin antihyperglycemic activity. Emtricitabine alone had not produced any significant effect on the blood glucose level in normal and diabetic rats. SDT, Single dose treatment; MDT, Multiple-dose treatment.

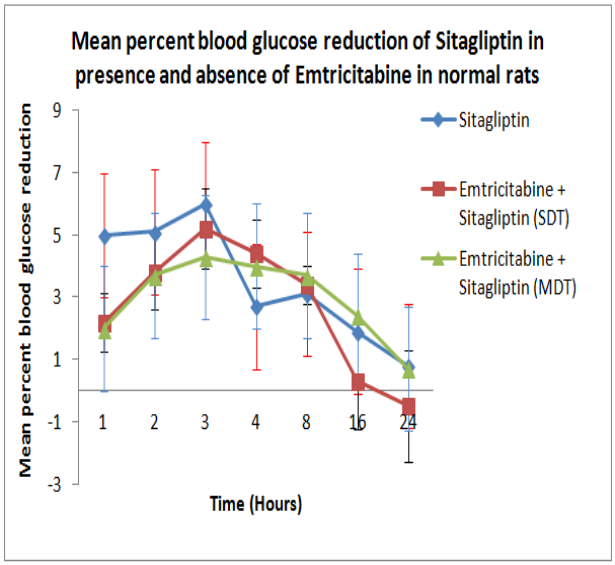

Figure 1

Table 1: Blood glucose levels (mg/dl) in rats treated with Sitagliptin alone and in the presence of Emtricitabine in normal rats (n=6)

Group	0 hr	1 hr	2 hr	3 hr	4hr	8 hr	16 hr	24 hr
Sitagliptin								
Blood glucose								
Mean	109.97	104.51	104.44	103.27	106.79	106.52	107.69	109.29
SD	5.29	7.45	8.51	8.28	5.56	4.84	4.87	11.42
%Reduction								
Mean	_	5.03	5.11	**6.04**	2.73	3.05	1.92	0.79
SD		3.04	4.73	7.01	6.64	4.49	6.20	6.41
Emtricitabine								
Blood glucose								
Mean	102.74	104.16	106.07	109.02	108.90	106.84	105.3	104.04
SD	1.92	1.85	1.47	2.57	3.34	2.80	2.48	2.59
%Reduction								
Mean	_	-1.38	-3.52	**-6.12**	-6.07	-3.98	-2.48	-1.26
SD		0.53	0.78	1.60	1.52	1.17	1.04	0.90
Emtricitabine +Sitagliptin (SDT)								
Blood glucose								
Mean	110.66	108.25	104.94	105.81	106.49	106.91	110.38	111.25
SD	2.39	1.98	3.46	3.55	4.58	1.76	4.66	5.58
%Reduction								
Mean	_	2.17	3.38	**5.15**	4.37	3.36	0.26	-0.52
SD		0.81	2.69	2.88	2.44	1.36	3.42	3.99
Emtricitabine +Sitagliptin (MDT)								
Blood glucose								
Mean	104.39	102.33	100.56	98.95	99.86	100.75	101.92	103.67
SD	1.89	2.37	1.72	2.02	2.12	2.11	2.01	2.21
% Reduction								
Mean	_	1.97	3.66	**4.34**	4.01	3.65	2.36	0.68
SD		0.89	1.07	1.17	1.82	1.15	0.77	1.34

Table 2: Blood glucose (mg/dl) levels in rats treated with Sitagliptin alone and in the presence of Emtricitabine in diabetic rats (n=6)

Group	0 hr	1 hr	2 hr	3 hr	4hr	8 hr	16 hr	24 hr
Sitagliptin								
Blood glucose								
Mean	263.62	229.80	203.06	132.86	183.54	196.86	220.66	257.54
SD	3.94	3.92	5.57	3.38	6.03	8.93	7.68	2.29
%Reduction								
Mean	_	12.84	23.00	**49.58**	30.36	25.34	16.34	2.28
SD		0.42	1.54	0.88	2.42	2.72	1.82	0.89
Emtricitabine								
Blood glucose								
Mean	255.60	265.00	274.40	279.41	287.60	272.80	265.79	256.60
SD	6.19	5.92	4.98	2.96	6.65	1.92	2.68	5.41
%Reduction								
Mean	_	-3.70	-7.38	**-9.36**	-12.56	-6.79	-4.03	-0.06
SD		2.43	1.71	2.96	3.06	3.03	2.11	1.33
Emtricitabine +Sitagliptin (SDT)								
Blood glucose								
Mean	262.98	228.70	199.32	135.42	174.44	192.04	219.22	256.84
SD	2.84	4.99	4.03	2.93	8.96	4.90	3.85	4.19
%Reduction								
Mean	_	13.03	24.20	**48.11**	33.66	26.96	16.63	1.89
SD		1.96	1.59	1.60	3.45	2.15	1.59	1.31
Emtricitabine +Sitagliptin (MDT)								
Blood glucose								
Mean	266.84	231.96	199.66	136.22	174.02	188.86	216.44	259.64
SD	1.29	4.24	5.09	3.86	4.66	5.77	4.46	1.59
%Reduction								
Mean	_	13.07	25.17	**49.0**	34.78	29.22	18.89	2.69
SD		1.24	1.86	1.34	1.73	2.44	1.42	0.79

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

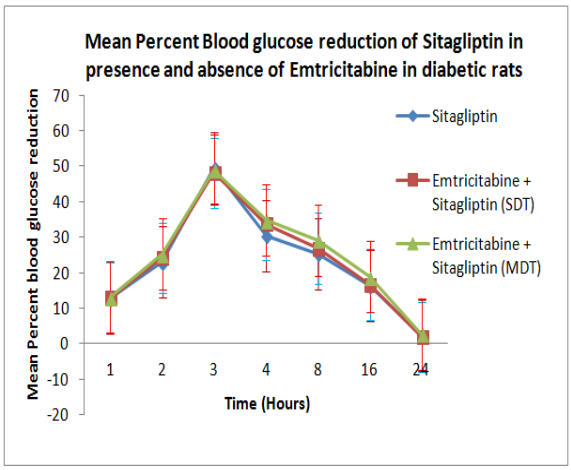

Figure 2

DISCUSSION

Frequently prescribed antiretroviral drugs belong to the class of nucleoside reverse transcriptase inhibitors (NRTIs) in HIV-infected patients. Emtricitabine is commonly used NRTIs for the treatment of HIV-infection.

However, there is no much evidence of emtricitabine effect alone in diabetic condition, as well as its influence on the activity of sitagliptin. Based on these factors the study was planned to investigate the effect of emtricitabine on blood glucose and its effect on the activity of sitagliptin in normal and diabetic rats.

In the present study, sitagliptin alone and in combination with single dose and multiple dose treatment of emtricitabine had not produced any antihyperglycemic activity in normal rats. In diabetic rats, sitagliptin produced significant antihyperglycemic activity. Upon acute and chronic administration of emtricitabine, emtricitabine did not interfere with antihyperglycemic activity of sitagliptin in diabetic rats. This confirms the absence of pharmacodynamic interaction.

CONCLUSION

Since there is no interaction between emtricitabine and sitagliptin in normal and diabetic rats, it is likely to be safe combination in humans also.

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