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RESEARCH ARTICLE

INFLUENCE OF NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (EMTRICITABINE) ON THE PHARMACODYNAMIC ACTIVITY OF SITAGLIPTIN IN ANIMAL MODELS

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ABSTRACT

The availability of potent combination of 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 (antiHIV drug) on pharmacodynamic activity of sitagliptin (antidiabetic drug) in normal and diabetic rats with respect to insulin levels. Alloxan-induced diabetic model in rats has been used in this study. In normal rats and diabetic rats the levels of insulin were calculated at 3 hr and 8 hr. The insulin levels were found to be similar in the groups of sitagliptin control and after single dose and multiple dose treatment of emtricitabine in normal rats. The insulin levels of diabetic rats did not reduce significantly in single and multiple dose treatment of emtricitabine when compared to sitagliptin control. The results confirm the absence of pharmacodynamic interaction of sitagliptin with acute and chronic administration of emtricitabine.

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INTRODUCTION

Polypharmacy is very common practice for the patients suffering with chronic diseases such as diabetes mellitus and HIV infection, and thus leads to the 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 (Pirmohamed, 2004; Huang, 2004), reveals that drug interactions played a vital role in reported adverse events and that majority of the drugs withdrawn for safety reasons from the US market were related with significant drug-drug interactions.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 (Huang, *et al*., 2008). 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 (Mastan, 2009 and Satyanarayana, 2006). Since many studies suggested that PI therapy (Hruz *et al*., 2006; Dube *et al*., 2000) is linked to the development of diabetic complications, it is of importance to propose therapeutic strategies with fewer side effects. 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. Nucleoside reverse transcriptase inhibitors are to be improving the metabolic complications in HIV-infected patients (Saag *et al*., 2002; Martinez *et al*., 1999).

In this contest, there are more chances of co administration of nucleoside reverse transcriptase inhibitors with oral hypoglycemic drugs in patients with concurrent type 2 diabetes mellitus and HIV infection which may leads to potent drug-drug interactions. Based on this background, formerly we have conducted a preliminary study (Lakshmi Rao, 2016) to investigate the effect of emtricitabine on the pharmacodynamic activity of sitagliptin in rats (normal and diabetic) with respect to blood glucose levels only. However, determination of insulin along with blood glucose levels would be a more precious and dependent approach to conclude a clear pharmacodynamic interaction scenario in the view of clinical and scientific stand-point.

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MATERIALS AND METHODS

Drugs and Chemicals

Sitagliptin and Emtricitabine were obtained as gift samples from Mylan Pharmaceuticals, Hyderabad and Aurobindo pharma Ltd. Hyderabad. Alloxan monohydrate was purchased from LOBA Chemie (Mumbai, India). Insulin kit (human insulin as standard; Insik-5, Sorin Biomedica, Saluggia, Italy).

Animals

Study was conducted on healthy Albino Wistar rats of either sex, weight range 200-250 g and rabbits of weight range of 1.5-2.0 kg. The animals were procured from Mahaveer enterprises, Hyderabad. All rats were kept for acclimatization for seven days prior to start the study. Animals were subjected to a constant daily cycle of 12 hours of light and 12 hours of darkness (06:00-18:00), constant temperature (21 ± 3 ºC) and relative humidity of 55 ± 15 %. Rats had access to commercial pelleted non-sterilised chow and normal tap water ad libitum, except during fasting access to food was restricted. Diabetes was induced in rats by the administration of alloxan monohydrate in two doses, i.e. 100 mg and 50 mg/kg bd. wt. intraperitoneally for two consecutive days (Heikkila, 1977). After 72 h, samples were collected from rats by orbital puncture of all surviving rats, and the serum was analyzed for glucose levels. Rats with blood glucose levels of 200 mg/dl and above were considered as diabetic and selected for the study. All the 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 and the experimental protocol has been approved by the IAEC.

Drug administration

Route of administration: Per oral

Vehicle: Antiretroviral drugs were suspended in sodium CMC for oral administration (Berruet, 2005). Sitagliptin solution was prepared by dissolving it in 5% gum acacia. All drugs were administered to respective groups by oral gavage method.

Experimental protocol

The rats were fasted for 18 hr prior to 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: Rats treated with sitagliptin (10 mg/kg/po)
Group- II: Rats treated with emtricitabine (3.6 mg/kg/po)
Group-III: Rats treated with emtricitabine (3.6 mg/kg/po) and sitagliptin (10 mg/kg/po)
Group-IV: 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 8 th day they received sitagliptin (10 mg/kg/po).

Blood samples were withdrawn from retro orbital plexus (Riley, 1960) of each rat was collected at time intervals of 3.0 and 8 hours.

Table 1. Insulin levels (µ u/ml) with Sitagliptin in presence and absence of Emtricitabine in normal and diabetic rats

Group	Normal Rats		Diabetic rats	
	3 hr	8 hr	3 hr	8 hr
Sitagliptin	9.92 ± 0.70	9.74 ± 0.90	11.49 ±0.66	10.78± 0.33
Emtricitabine	8.54 ± 0.52	8.30 ± 0.35	2.24 ± 0.18	2.14 ± 0.24
Emtricitabine+ Sitagliptin(SDT)	9.52± 0.27	9.44 ± 0.13	11.04 ±0.65	10.72 ± 0.55
Emtricitabine + Sitagliptin (MDT)	9.38 ± 0.34	9.26 ± 0.27	10.92 ±0.44	10.66 ± 0.47

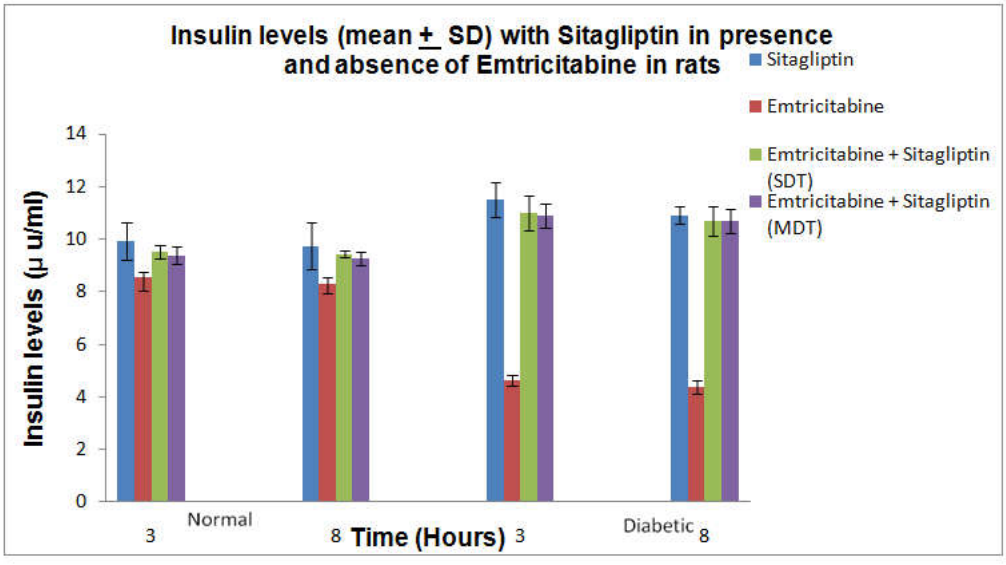

Figure 1.

The collected plasma was used to determine insulin levels by Radioimmunoassay method (Mastan, 2010) using a commercially available kit (Biomedica, Saluggia, Italy) as per the instructions provided by the manufacturers.

Data and statistical analysis

Data were expressed as mean ± SEM. The significance was determined by applying Student's paired 't' test.

RESULTS AND DISCUSSION

Effect of Emtricitabine on Sitagliptin with respect to Insulin levels

In normal and diabetic rats the levels of insulin were calculated at 3 hr and 8 hr. The insulin levels were found to be similar in the groups of sitagliptin control and after single dose and multiple doses of emtricitabine (Table 1 and Figure 1). Emtricitabine alone had no significant effect on insulin levels in normal and diabetic rats. HIV infected patients are likely to suffer with diabetes mellitus and hence most often antiretroviral drugs are coadministered along with oral antidiabetic drugs. HIV infection and diabetes are both chronic diseases that significantly affect lifestyle. When they intersect, the treatment regimens required for both diseases can be overwhelming for pateints. 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. Nucleoside reverse transcriptase inhibitors are to be improving the metabolic complications in HIV-infected patients (Saag, 2002; Martinez, 1999). However, there is no much evidence on the activity of emtricitabine alone in diabetic condition, as well as its effect on the activity of sitagliptin. Based on these factors the study was planned to investigate the effect of emtricitabine on insulin levels and its effect on the activity of sitagliptin in normal and diabetic rats to evaluate the pharmacodynamic interaction with respect to insulin levels. In this study, the multiple dose effect of emtricitabine on the sitagliptin activity was also studied for the influence of the long term treatment with emtricitabine since both drugs are used for chronic period. The normal rat model served to quickly identify the interaction and diabetic rat model served to validate the same response in the actually used condition of the drug. In diabetic rats, sitagliptin produced significant antihyperglycemic activity. Upon acute and chronic administration of emtricitabine did not interfere with antihyperglycemic activity of sitagliptin in diabetic rats. Our study revealed the safety profile of emtricitabine with respect to insulin levels. It confirms the absence of pharmacodynamic interaction between emtricitabine and sitagliptin.

Conclusion

The combination of emtricitabine and sitagliptin was proved to be safe for clinical benefit.

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