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INFLUENCE OF SITAGLIPTIN ON PHARMACOKINETICS OF RALTEGRAVIR IN RATS

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ABSTRACT

As antiretroviral therapy becomes increasingly accessible, the associated improvements in the health, quality of life and survival of patients. 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 sitagliptin (antidiabetic drug) on pharmacokinetics of raltegravir (antiHIV drug) in rats. The pharmacokinetic parameters like $t_{1/2}$, AUC, Clearance, Tmax and Cmax of raltegravir with and without combination of sitagliptin treatment was determined. The plasma concentration-time profiles of raltegravir following single dose and multiple dose treatment of sitagliptin were found to be dissimilar. There was change in the pharmacokinetic parameters in presence of sitagliptin indicates the significant ($p>0.05$) pharmacokinetic interaction.

KEYWORD: Raltegravir, sitagliptin, pharmacokinetics.

1. INTRODUCTION

Patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are increasing in number, partly due to improved screening, earlier diagnosis, better methods of treatment, and greater accessibility to, as well as acceptance of therapy. Figures from the United Nations reveal that the total number of patients with HIV is 33 million, with 2.7 million new infections in 2007[1]. Impaired glucose tolerance, and insulin resistance are noted to precede weight loss in patients with HIV[2-6]. Type -2 diabetes may occur as a result of HIV infection and/or its treatment. Many metabolic perturbations that occur as a result of HIV- infection and its treatment, alterations in normal glucose homeostasis remain particularly prevalent and alarming clinical changes in affected patients[7]. Diabetes mellitus is one such metabolic disorder that requires drug treatment for prolonged periods[8]. The study of mechanisms of drug interactions is valuable when selecting the drug concentrations that provide rational therapy.

2. MATERIALS AND METHODS

Raltegravir and Sitagliptin drugs were gifted by Lupin Pharma, Pune and Mylan laboratories, Hyderabad, respectively. Study was conducted on healthy albino wistar rats of either sex, weight range 200-250 g. The animals were procured from Mahaveer enterprises, Hyderabad. All rats were kept for acclimatization for seven days prior to start the study and was maintained at 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 %. The study drugs were administered with oral feeding tube at Sitagliptin 10 mg/kg & Raltegravir 7.2 mg/kg body weight.

Experimental study design

The study was conducted in albino wistar rats of either sex weight range 200-250 gms were suitably divided in three groups of six rats each.

Group-I: Normal rats treated with raltegravir 7.2 mg/kg/p.o

Group-II: Normal rats treated with sitagliptin 10 mg/kg/p.o and raltegravir 7.2 mg/kg/p.o

Group-III: Normal rats treated with sitagliptin 10 mg/kg/p.o treatment was continued for 7 days and on 8 day treated with raltegravir 7.2 mg/kg/p.o.

Collection of blood samples

Blood samples was collected from each animal at time interval of 0.0, 1.0, 2.0, 3.0, 4.0,8.0, 16.0 and 24.0 hours after dosing by retro orbital puncture of rats eye using a capillary tube of size 3 inches. Plasma was separated after centrifugation for 15 minutes at 4000rpm.The collected plasma was stored at -20^0 c and was used to quantify raltegravir after extraction.

Analysis of plasma Raltegravir concentrations

All the collected blood samples in single and multiple day study were analysed for raltegravir concentration using developed HPLC method[9].

Statistical Analysis

All the experimental values were expressed as mean ±

SD. Pharmacokinetic analysis by non compartmental method using WinNonlin software.

3. RESULTS

The effect of sitagliptin on pharmacokinetics of raltegravir was studied in single and multiple day interaction. The blood samples from all the groups of rats at different intervals and were analyzed for raltegravir concentrations and the results of estimated pharmacokinetic parameters were shown in table -1 and fig-1.

Single dose interaction study

The plasma raltegravir concentrations in the groups of raltegravir alone and in combination with sitagliptin were found to be dissimilar and statistically significant difference was observed.

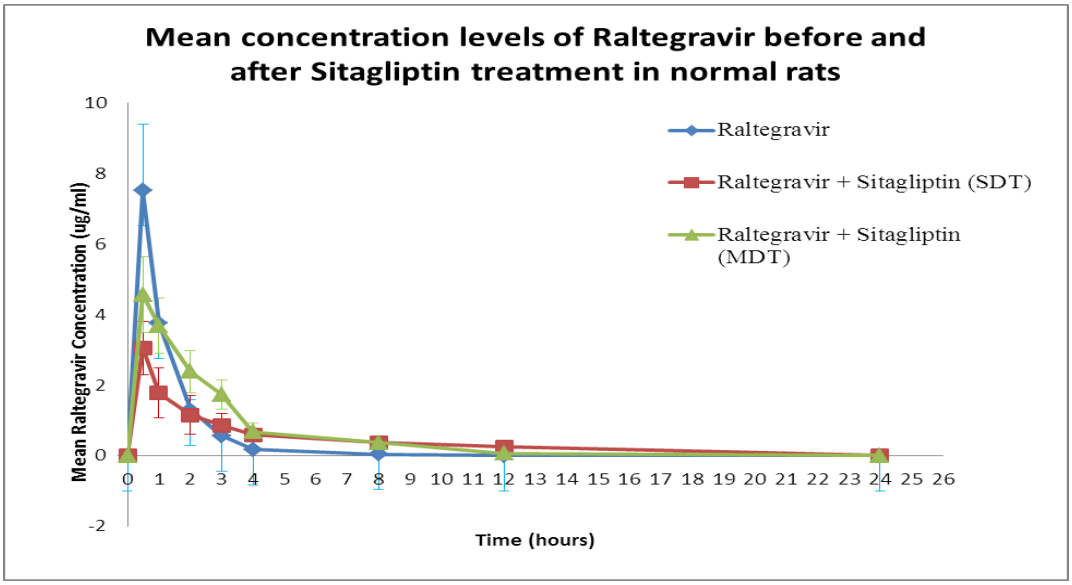
Multiple Dose interaction study

The plasma raltegravir concentrations in the groups of raltegravir alone and in combination with sitagliptin were found to be dissimilar and statistically significant difference was observed.

Table 1.1 Pharmacokinetic parameters (Mean ± SD) of Raltegravir in presence and absence of Sitagliptin in normal rats

PK parameters	Raltegravir	Sitagliptin + Raltegravir (SDT)	Sitagliptin + Raltegravir (MDT)
Tmax(hr)	0.5± 0.0	0.5 ± 0.0	0.5 ± 0.0
Cmax (ug/ml)	7.52 ± 1.86	3.05 ± 0.77***	4.57± 1.07 **
AUC0-t ug.hr/ml)	8.94 ± 1.35	8.27 ± 2.33	12.34 ± 2.45*
AUC0-∞(ug.hr/ml)	9.02 ± 1.34	10.72± 2.98	12.67± 2.34*
MRT hr	1.28 ± 0.10	3.68± 0.28***	2.65± 0.48***
Kel hr^{-1}	0.61 ± 0.14	0.64 ± 0.24	0.37 ± 0.09
T1/2 hr	1.21 ± 0.35	1.08 ± 1.88	1.96 ± 0.43
Vd L	4.90 ± 1.37	4.51± 2.42	5.73± 1.61
Cl L/hr	2.82 ± 0.41	2.04 ± 1.02	2.04 ± 0.42

SDT, single dose treatment; MDT, Multiple-dose treatment;
***significant at p <0.001, **significant at p <0.01 *significant at p<0.05



4. DISCUSSION

HIV and diabetes are both chronic diseases that significantly affect lifestyle. When they intersect, the treatment regimens required for both diseases can be overwhelming for patients. Several studies have reported a prevalence of diabetes of 2% to 7% among HIV-infected patients receiving protease inhibitors[10]. The incidence of diabetes mellitus in HIV-infected patients has been estimated to range from 1% to 10% in various studies[10]. However, in our present study we investigated the effect of sitagliptin on the pharmacokinetic activity of raltegravir. In this study, the multiple doses of sitagliptin on raltegravir pharmacokinetics were studied to determine the influence of long treatment with sitagliptin since both are used for chronic conditions. Drug interactions are often seen in clinical practice and the mechanisms of such interactions are often evaluated in animal models. Although animal model can never replace the need for comphrensive human trials, the use of animal model can provide important insights in understanding and evaluation of potent drug interaction.

This study revealed that there is pharmacokinetic

interaction between sitagliptin and raltegravir in normal rats. Sitagliptin decreased Cmax of raltegravir in single dose treatment and multiple doses treatment. Upon chronic administration slight increase in AUC indicating that sitagliptin is interfering with bioavailability of raltegravir.

The pharmacokinetic drug interaction observed during co-administration of sitagliptin and raltegravir could possibly be due to in-vivo interaction of two moieties which are salt of either strong acid (sitagliptin phosphate) or strong base (raltegravir potassium) however they themselves are weak base and weak acid with limited solubility in aqueous physiological environment. In study raltegravir solubility, lipophilicity, pK_a, and permeativity *in vitro* studies elucidated known interactions with antacids, and food, all of which increase gastric pH. Raltegravir lipophilicity was pH dependent and was reduced as pH was increased from 5 to 9. The pK_a of raltegravir was 6.7. Raltegravir cellular permeativity was heavily influenced by changes in extracellular pH, where apical-to-basolateral permeativity was reduced 9-fold ($P < 0.05$) when apical pH was increased from 5 to 8.5. Raltegravir cellular permeativity was also reduced in the presence of magnesium and calcium[11]. Our results are in agreement with this literature. This observation is required to be investigated further to confirm and understand principles responsible for alteration in Cmax and AUC of raltegravir in presence of sitagliptin.

CONCLUSION

The results confirmed the presence of pharmacokinetic interaction of raltegravir with sitagliptin at absorption level. Raltegravir, which may need dosage adjustment. Hence care should be taken when this combination is prescribed for clinical benefit. This study should be further investigate by using dissimilar species and understand principles responsible for alteration in plasma concentration of raltegravir in presence of sitagliptin to confirm the occurrence of interaction in order to extrapolate to humans.

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