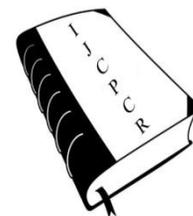




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DRUG INTERACTION OF RABEPRAZOLE ON SULFONYLUREAS IN DIABETIC RATS

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ABSTRACT

The influence of larger dose of pretreatment for seven days on the anti diabetic effect of glibenclamide and glipizide was studied. This study was conducted on alloxan induced diabetic rats of either sex, randomly distributed into 4 different groups. The first two groups were treated with acacia suspension 2% w/v and rabeprazole 40 mg/kg, p.o in 2% w/v gum acacia suspension for seven days and the other two groups (3 and 4) were treated with glibenclamide and glipizide respectively. The animals of the same groups were pretreated with rabeprazole (40 mg/kg) for 7 days. On eighth day, glibenclamide (200 µg/kg, p.o) and glipizide (200 µg/kg, p.o) were administered to respective groups one hour after treatment. Blood samples were collected from retro-orbital sinus at time intervals of 00, 1, 2, 4, 8, 12, 18, and 24 hrs and plasma glucose levels were estimated by GOD/POD method. The onset of glucose reduction, peak effect and duration of action were assessed. The study indicated that higher dose (around 8 times of therapeutic dose) of rabeprazole pretreatment has enhanced the anti diabetic effect of glibenclamide and glipizide significantly. Hence it is suggested that there is no possibility of occurrence of drug interaction during the concomitant usage of therapeutic doses of rabeprazole and sulfonylureas. Therefore the therapeutic drug monitoring and readjustment of the dose and frequency of administration of sulfonylureas are not essential at therapeutic dose levels.

Key words: Rabeprazole, glibenclamide, glipizide, alloxan, antidiabetic activity.

INTRODUCTION

There are several incidences that a patient may suffer with more than one disease at a time. It is a need to treat all his ailments simultaneously. Hence it may require administering more than one drug at a time. In such instances, the potential for drug interactions is therefore substantial and polypharmacy is an important factor to be considered when prescribing for a prolonged period. According to reports, the risk of drug interaction increases exponentially with the no of drugs given to a patient [1]. It is the fourth to sixth leading cause for death in United States [2]. Diabetes mellitus is a disease characterized by elevated blood glucose levels and requires treatment for lifelong. Diabetic patients may also be affected with many other diseases like peptic ulcer, fungal infections and hypertension. All these diseases are also require treatment

for chronic period/ life-time. The reports reveal that about 7% of diabetic patients are suffering from peptic ulcers [3]. There are several patients who are suffering with both diabetes and peptic ulcer. In such patients proton pump inhibitors like rabeprazole, and sulfonylureas like glibenclamide and glipizide were administered concomitantly. There are reports that rabeprazole is known to inhibit cytochrome P-450 enzyme system [4], hence there is a possibility of occurrence of pharmacokinetic type of drug interactions with concomitantly used drugs. Glibenclamide and glipizide are metabolized by cytochrome P-450 enzyme system [5, 6]. Therefore the present study was conducted in diabetic rats to assess the influence of rabeprazole pretreatment on the anti diabetic effects of sulfonylureas like glibenclamide and glipizide.

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MATERIALS AND METHODS**Animals**

The study was conducted on diabetic rats (wistar strain) of either sex weighing 200-260 g. The animals were randomly distributed into 4 groups of 6 animals each. The albino rats were procured from Sri Venkateshwara Enterprises, Bangalore. The animals were housed under ambient temperature of $28 \pm 2^\circ\text{C}$ and $50 \pm 2\%$ relative humidity with 12 hr light / 12 hr dark cycle. Prior approval by institutional ethics committee (Ref No. **IAEC / XIII / 05 / SRCP / 2011**) was obtained for conduction of experiments. The study was conducted in Smt. Sarojini Ramulama College of Pharmacy, Mahabub Nagar, Andhra Pradesh-509 001.

Drugs

Glibenclamide and glipizide were obtained from Cipla, Mumbai and rabeprazole was obtained from Dr. Reddy's labs ltd. Hyderabad. Glibenclamide (200 $\mu\text{g}/\text{kg}$, p.o), glipizide (200 $\mu\text{g}/\text{kg}$, p.o) and rabeprazole (40 mg/kg, p.o for 7 days) suspensions were prepared by using 2% w/v gum acacia as a suspending agent.

Experimental**Induction of diabetes in rats**

Diabetes was induced in the rats by administering 120 mg/kg of Alloxan intraperitoneally into the 24 hr fasted rats [7]. Blood samples were collected after 24 hrs and blood glucose levels were estimated. Albino rats which have shown more than 200 mg/dl blood glucose levels were considered as diabetic. The blood glucose levels were monitored for further four days. From this it was confirmed that diabetes was induced in 24 hrs and stabilized within 4 days. These animals were used for further studies.

The diabetic rats were marked conveniently and randomly distributed into four groups of 6 animals each. All the animals were over night fasted with water *ad libitum*. The animals in group-1 received 2% w/v acacia suspension and the animals in the group- 2 received rabeprazole (40 mg/kg, p.o) in acacia suspension. Group-3 received glibenclamide (200 $\mu\text{g}/\text{kg}$, p.o) and group-4

received glipizide (200 $\mu\text{g}/\text{kg}$, p.o). Blood samples were collected at 0.0, 1.0, 2.0, 4.0, 8.0, 12.0, 18.0, 24.0 hr after treatment by retro-orbital sinus in mild anaesthetized rats. Blood glucose levels were estimated by GOD/POD method and expressed as mg/100 ml of blood. In the next phase of the experiment, the animals of group-3 and 4 received rabeprazole 40 mg/kg, p.o for seven days. On the 7th day, 6 hours after administration of rabeprazole, the animals were fasted for 14 hours. On the 8th day, rabeprazole was given as usual. One hour after the treatment, animals of group-3 received glibenclamide 200 $\mu\text{g}/\text{kg}$, p.o and group-4 received glipizide 200 $\mu\text{g}/\text{kg}$, p.o. Blood samples were collected thereafter at above mentioned intervals and glucose levels were estimated. The % blood glucose reduction at various time intervals were calculated and compiled in Table 1.

Statistical analysis

The data were expressed as mean \pm standard error mean (S.E.M).The Significance of differences among the group was assessed using one way and multiple way analyses of variance (ANOVA). The test followed by Dunnet's test p values less than 0.05 were considered as significance.

RESULTS

It is evident from the table 1 that, treatment with acacia suspension alone has not influenced the blood glucose levels in diabetic rats. Rabeprazole *per se* did not alter the blood glucose levels. However, pretreatment with rabeprazole 40 mg/kg, p.o has not significantly altered the onset of antidiabetic effect of glibenclamide and significantly enhanced peak antidiabetic effect from 40.12 ± 1.21 at 4th hr to 57.56 ± 1.19 at 4th hr and duration of antidiabetic effect was raised from 17 hrs to 23 hrs. Whereas pretreatment with rabeprazole 40 mg/kg, p.o has significantly altered the onset of antidiabetic effect of glipizide and enhanced the peak antidiabetic effect from 35.58 ± 1.48 to 47.61 ± 1.03 at 2nd hr. Duration of antidiabetic effect was slightly altered.

Table 1. Percentage decrease in blood glucose levels at different time intervals (Following various treatments in diabetic albino rats)

Time in Hrs	Acacia suspension	Rabeprazole (40 mg/kg, p.o.)	Glibenclamide (200 $\mu\text{g}/\text{kg}$, p.o.)	Rabeprazole (40 mg/kg, p.o, 7 days)+Glibenclamide (200 $\mu\text{g}/\text{kg}$, p.o.)	Glipizide (200 $\mu\text{g}/\text{kg}$, p.o.)	Rabeprazole (40 mg/kg, p.o, 7 days) +Glipizide (200 $\mu\text{g}/\text{kg}$, p.o.)
Fasting	-	-	-	-	-	-
1.0	-2.24 ± 1.25	0.12 ± 1.22	20.12 ± 1.26	21.52 ± 1.16	13.58 ± 2.44	$23.19 \pm 1.03^{**}$
2.0	0.23 ± 0.25	-0.15 ± 0.29	36.12 ± 1.28	47.59 ± 1.15	35.58 ± 1.48	$47.61 \pm 1.03^{**}$
4.0	-7.27 ± 7.28	-3.17 ± 1.29	40.12 ± 1.21	$57.56 \pm 1.19^*$	34.59 ± 1.49	$46.41 \pm 3.17^*$
8.0	-0.25 ± 1.24	-3.15 ± 0.21	35.12 ± 2.24	$58.53 \pm 1.15^{**}$	32.53 ± 1.42	34.13 ± 3.01
12.0	-0.24 ± 0.29	-1.12 ± 0.23	27.12 ± 1.27	$53.59 \pm 1.13^{***}$	24.56 ± 1.42	21.14 ± 1.05
18.0	-1.29 ± 0.27	2.13 ± 1.01	21.12 ± 1.24	$42.57 \pm 1.71^{***}$	15.51 ± 1.46	16.02 ± 1.08
24.0	0.27 ± 1.23	0.19 ± 1.04	7.02 ± 1.15	$31.59 \pm 1.41^{***}$	7.14 ± 0.74	6.16 ± 1.19

$n=6$. * Significant at $p < 0.05$; ** highly significant at $p < 0.01$; *** very highly significant at $p < 0.001$

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder which requires treatment for life long. Peptic ulcer is one such disease which requires treatment for a prolonged period. If a patient is suffering with diabetes mellitus and peptic ulcer, we may have to use anti diabetic drugs such as sulfonylureas like glibenclamide and glipizide and proton pump inhibitors like rabeprazole. In such situations, there is a possibility of occurrence of drug interactions. Our pilot study has indicated that drug interactions do not occur when rabeprazole and glibenclamide/glipizide is administered concomitantly at therapeutic doses [8]. Attempts were made to assess the influence of higher doses of rabeprazole on anti diabetic effect of sulfonylureas. It was observed that 8 times that of the therapeutic dose required to significantly altering the effects of sulfonylureas. For the assessment of the potentiation of anti diabetic effect, onset of action, (time taken to reduce minimum of 20% reduction in blood glucose levels), peak effect, duration of anti diabetic effect (duration in which minimum of 20% reduction in blood glucose levels are maintained) were considered.

Since rabeprazole (40 mg/kg) *per se* did not influenced the blood glucose levels and the possibility of occurrence of pharmacodynamic interaction can be ruled out. In our study, pretreatment with rabeprazole did not alter the onset of action of glibenclamide. However, peak

effect and duration of anti diabetic effect induced by glibenclamide is significantly enhanced. In case of pretreatment with rabeprazole the onset, peak effect and duration of action of glipizide were increased significantly. These findings suggest that rabeprazole may interfere with the absorption of glipizide. It may be inferred from the results that rabeprazole has retarded their metabolism by inhibiting the enzymes responsible for their metabolism. There are reports that both glibenclamide and glipizide are mainly metabolized by CYP2C9 and CYP3A4 [9-13]. Reports also indicate that rabeprazole is having lower affinity for cytochrome P 450 system [14]. It is evident from the results that 8 times the therapeutic dose of rabeprazole enhanced the anti diabetic effect of both the sulfonylureas. This may be due to weak inhibitory effect of rabeprazole on CYP2C9 and CYP3A4. Further studies are undertaken to establish the influence of rabeprazole pretreatment on the pharmacokinetic parameters of sulfonylureas.

CONCLUSION

Since 8 times of therapeutic dose of rabeprazole has influenced the anti diabetic effect of sulfonylureas, it may be concluded that during the concomitant administration of sulfonylureas and rabeprazole at therapeutic doses, the dose and frequency of administration of sulfonylureas need not be readjusted.

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