INFLUENCE OF RABEPRAZOLE ON ANTIDIABETIC EFFECT OF SULFONYLUREAS IN DIABETIC RATS

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Summary

The influence of larger dose of rabeprazole pretreatment for seven days on the anti diabetic effect of glibenclamide and glipizide was studied. This study was conducted on alloxan (120mg/kg, i.p.) 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 30 mg/kg, p.o in 2% w/v gum acacia for seven days and the other two groups (3 and 4) were treated with glibenclamide (200 µg/kg) and glipizide (200 µg/kg) respectively. The blood samples were collected from retro-orbital sinus and blood glucose levels were determined. The onset of glucose reduction, peak effect and duration of action were assessed. The animals of the same groups were pretreated with rabeprazole 30 mg/kg) for 7 days. On eighth day sulfonylureas were administered to respective groups one hour after rabeprazole treatment. Blood samples were collected from retro-orbital sinus at frequent time intervals and plasma glucose levels were estimated by GOD/POD method.

The study indicated that higher dose (around 16 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 (glibenclamide and glipizide). Therefore the therapeutic drug monitoring and readjustment of the dose and frequency of administration of sulfonylureas (glibenclamide and glipizide) are not essential when these two classes of drugs are used concomitantly at therapeutic dose levels.

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

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Introduction

The potential for occurrence of drug interactions is substantial in polypharmacy and this is one important factor to be considered while prescribing multiple drugs for a chronic 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 disorder 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. There are reports that several patients who are suffering with both diabetes and other diseases including peptic ulcers. The reports reveal that about 7% of diabetic patients are suffering from peptic ulcers[3]. In such patients proton pump inhibitors like omeprazole, rabeprazole or pantaprazole and sulfonylureas like glibenclamide or glipizide are 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.

Materials and Methods

Animals

The study was conducted on diabetic rats (wistar strain) of either sex, weight range 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 ± 2ºC and 50 ± 2% relative humidity with 12 hr light / 12 hr dark cycle. Prior approval by institutional ethics committee (reg. no: 157/99/CPCSEA) was obtained for conduction of experiments. The study was conducted in the Department of Pharmacology of S.C.S. College of Pharmacy Harapanahalli between 2007 and 2008.

Drugs

Glibenclamide and glipizide were obtained from Cipla, Mumbai and rabeprazole was obtained from Dr. Reddy's labs ltd. Hyderabad.
Glibenclamide (200 µg/kg, p.o), glipizide (200 µg/kg, p.o) and rabeprazole (30 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 mellitus

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 (30 mg/kg, p.o) in acacia suspension. Group-3 received glibenclamide (200 µg/kg, p.o) and group-4 received glipizide (200 µg/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[8] and expressed as mg/100 ml of blood.

In the next phase of the experiment, the animals of group-3 and 4 received rabeprazole 30 mg/kg, p.o for seven days. On the 7^{th} day, 6 hours after administration of rabeprazole, the animals were fasted for 14 hours. On the 8^{th} day, rabeprazole was given as usual. One hour after the treatment, animals of group-3 received glibenclamide 200 µg/kg, p.o and group-4 received glipizide 200µg/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 was analyzed by Student Newman kleus test. P values lower than 0.05 were considered as statistically significant.

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 *perse* did not alter the blood glucose levels. However, rabeprazole pretreatment 30 mg/kg, p.o has not significantly altered the onset of antidiabetic effect of glibenclamide and significantly enhanced peak antidiabetic effect from 45.67 ± 2.02 % at 4^{th} hr to 54.27 ± 3.89 % at 8^{th} hr and duration of antidiabetic effect was raised from 17 hrs to 22 hrs.

Where as preatreatment with rabeprazole 30 mg/kg, p.o has not significantly altered the onset of antidiabetic effect of glipizide but enhanced peak antidiabetic effect from 46.69 ± 2.25 % to 51.6 ± 2.37 %. Duration of antidiabetic effect was slightly altered.

Table No. 1 Percentage decrease in blood glucose levels at different time intervals (Following various treatments in diabetic albino rats)

	% reduction in blood glucose concentration, Mean ± SEM					
Time in Hrs	Acacia suspension	rabeprazole (30 mg/kg, p.o,)	Glibenclamide (200 µg/kg, p.o,)	rabeprazole (30 mg/kg, p.o, 7 days) + Glibenclamide (200 µg/kg, p.o,)	Glipizide (200 µg/kg, p.o,)	rabeprazole (30 mg/kg, p.o, 7 days) + Glipizide (200 µg/kg, p.o,)
Fasting	---	---	---	---	---	---
1.0	-2.04 ± 1.05	0.65 ± 0.94	20.16 ± 1.3	14.55 ± 2.96	16.42 ± 2.72	18.95 ± 3.28
2.0	0.83 ± 0.85	-0.58 ± 1.28	39.9 ± 2.46	45.98 ± 2.79	45.92 ± 1.98	51.6 ± 2.37
4.0	-7.47 ± 7.38	0.25 ± 1.82	45.67 ± 2.02	53.10 ± 2.19	46.69 ± 2.25	48.68 ± 4.24
8.0	-0.65 ± 1.64	-4.65 ± 3.31	40.95 ± 2.38	54.27 ± 3.89**	39.06 ± 1.97	45.71 ± 3.07
12.0	-0.34 ± 0.79	-2.52 ± 1.22	34.22 ± 2.29	48.99 ± 4.87*	28.05 ± 2.65	37.38 ± 2.67*
18.0	-1.29 ± 0.57	-2.04 ± 2.1	23.58 ± 2.28	38.90 ± 5.69*	19.58 ± 2.44	29.31 ± 2.65*
24.0	0.57 ± 1.03	0.61 ± 1.65	11.91 ± 2.58	25.0 ± 5.21	9.29 ± 2.22	17.28 ± 2.68*

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 lifelong. 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 are administered concomitantly at therapeutic doses. The increasing doses of rabeprazole was tried to assess the influence on the anti diabetic effects. However, 16 times that of the therapeutic dose was found to influence the anti diabetic effect significantly.

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 (30 mg/kg) *perse* 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 (30 mg/kg) did not alter the onset of action of sulfonylureas, however peak effect and duration of anti diabetic effect induced by sulfonylureas are significantly enhanced. These findings suggest that rabeprazole do not alter the absorption of sulfonylureas. Rabeprazole pretreatment has increased the peak effect and duration of action of sulfonylureas. This suggests 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 a weak inhibitor of CYP3A4, CYP2C9, CYP2C19 and CYP2D6[14] among all proton pump inhibitors. It is evident from the results that 16 times of 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.

Our studies in diabetic rats suggested that drug interaction occurs between rabeprazole and sulfonylureas when they are used concomitantly in pathophysiological conditions like diabetes mellitus at very high dose.

In the present study, results indicate that during the concomitant administration of sulfonylureas and rabeprazole at therapeutic doses, the dose and frequency of administration of sulfonylureas need not be readjusted. However, blood glucose levels may be monitored during that period as precautionary measure so as to avoid severe hypoglycaemia.

Conclusion

It may be concluded that 16 times that of therapeutic dose of rabeprazole is required to influence the effect of sulfonylrureas and hence there is no need to readjust the dose and frequency of administration of them when they are used concomittantly at therapeutic doses.

Acknowledgement

We would like to thank Sri. Sha.Bra.Chandramouleshwara Swamiji, the president and Sri. T.M.Chandrashekharaiah, the secretary, T.M.A.E Society for providing all the facilities to carry out this research work.

We also thank Cipla, Mumbai for providing glibenclamide and glipizide and Dr. Reddy's labs. Hyderabad for providing pantoprazole.

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