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Influence of Lansoprazole on Hypoglycaemic Activity of Oral Antidiabetic Agents in Healthy Albino Rats

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Abstract

Drug interaction between sulfonylureas (Tolbutamide and glibenclamide) and lansoprazole (anti-ulcer drug) was studied in healthy albino rats and diabetic rats (alloxan induced diabetes). Hypoglycaemia (onset, Peak effect and duration) induced by tolbutamide (40 mg/kg, po) and glibenclamide (40 µg/kg, po) in rats was observed. Tolbutamide has produced hypoglycaemia to the extent (peak effect) of about 52.60% ± 2.64, onset of action was about 2 hrs and duration was about 34hrs. Similarly the extent of hypoglycaemia induced by glibenclamide was about 52.15% ± 2.07, onset of action was about 2hrs and duration was more than 46 hrs. The same group of animals was given with lansoprazole 60 mg/kg for one week and then parameters of hypoglycaemia induced by above-mentioned sulfonylureas was observed on the 8th day. Pretreatment with lansoprazole has enhanced the duration of hypoglycaemia induced by tolbutamide i.e 46 hrs, peak effect slightly i.e. 57.10% ± 1.81 whereas onset of action was not altered significantly. Similarly lansoprazole pretreatment has enhanced the peak effect and duration of hypoglycaemia induced by glibenclamide. In diabetic animals also similar influence of lansoprazole on hypoglycaemia induced by sulfonylureas was observed. Hence, it is suggested that during the concomitant usage of lansoprazole and sulfonylureas, the therapeutic drug monitoring is essential and may also require readjusting the dose and frequency of administration of sulfonylureas.

Key Words: Lansoprazole, tolbutamide, glibenclamide, hypoglycaemic activity.

Introduction

Diabetes mellitus is a disease characterized by elevated blood glucose levels and requires treatment for chronic period or life long. Diabetic patients may also be affected with many other diseases like peptic ulcers, infectious diseases etc. During such conditions, treatment for all the ailments should be given simultaneously. Peptic ulcer is one such disorder, which also require treatment for a prolonged period. There are several patients who are suffering with both diabetes and peptic ulcer. In such patients H_2-receptor blockers or proton pump inhibitors and sulfonylureas or insulin preparations are administered concomitantly. There are reports that H_2-receptor blockers like ranitidine inhibit the metabolism of sulfonylureas and enhance their bio-availability (Kubacka *et al.*, 1987; Stephen and Daryl, 1996). Similarly there are reports that chronic usage of omeprazole increases the peak concentration and apparent elimination half-life of phenytoin in healthy male volunteers (Prichard *et al.*, 1987). In addition, there is one report that omeprazole increased the duration and peak effect of hypoglycaemia induced by

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sulfonylureas in healthy albino rabbits (Vikas Kumar *et al.,* 2000). However there is one report that proton pump inhibitors like lansoprazole has induced cytochrome - P450 enzyme system (Meyer, 1996). These reports are confusing and are contradictory to each other. In addition, there are no reports regarding the influence of lansoprazole pretreatment on the effect/pharmacokinetics of sulfonylureas. Hence the present study was conducted in healthy albino rats and diabetic rats to assess the influence of lansoprazole pretreatment on the hypoglycaemia induced by sulfonylureas (tolbutamide and glibenclamide).

Materials and Methods

Animals: The study was conducted on healthy albino rats of either sex weighing between 150 - 200 g and rats were procured from the central animal house, V.L. College of Pharmacy, Raichur. The animals were randomly distributed into different groups. The animals were kept in colony cages at ambient temperature of 27° ± 2° C and 45 – 55 % relative humidity with a 12 hour light/12 hour dark cycle.

Lansoprazole was obtained from M/s Dr. Reddy's Laboratories, Hyderabad and Cipla Ltd., Bangalore, Glibenclamide from Hoechst India Ltd., Mumbai and Tolbutamide from Albert David, Mumbai.

Preparation of drugs for treatment: All the drugs of the study [lansoprazole (60 mg/kg, p.o. for seven days), glibenclamide (40 µg/kg, p.o.) and tolbutamide (40mg/kg, p.o.)] were suspended separately in 5% acacia suspension in distilled water. Acacia suspension (5% in water) was used as control.

Experimental Procedure: Healthy albino rats were suitably marked and randomly distributed into four groups. All the animals were fasted for 18 hours with water *ad libitum*. Animals of group 1 and 2 were administered with tolbutamide (40 mg/kg, p.o.) and group 3 and 4 received glibenclamide (40 µg/kg, p.o.). Blood samples were collected from the tail vein at 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 30, 36, 42, 48 hours and blood glucose levels were estimated by GOD/POD method (Trinder, 1969). In the next phase of the experiment, the animals of Group 1 and 3 received acacia suspension (0.5 ml/day for seven days) and served as control and the animals of group 2 and 4 received lansoprazole 60 mg/kg/day for seven days. On the seventh day 6 hours after lansoprazole administration, the animals were fasted for 18 hours and water was given *ad libitum*. On the eighth day lansoprazole / acacia suspension were given as usual. One hour after the treatment, animals of group 1 and 2 received tolbutamide and group 3 and 4 received glibenclamide. 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.

Table 1. Effect of Lansoprazole on tolbutamide and glibenclamide induced hypoglycaemia in healthy rats.

Time in hrs.	% blood glucose reduction by tolbutamide before and after lansoprazole treatment (60 mg/kg)		% blood glucose reduction by glibenclamide before and after lansoprazole treatment (60 mg/kg)	
	Before	After	Before	After
Fasting	- - -	- - -	- - -	- - -
0.5	05.62 ± 2.18	08.24 ± 1.95	04.89 ± 1.18	08.13 ± 1.46
1.0	10.44 ± 0.90	14.92 ± 2.23	13.18 ± 1.46	15.74 ± 1.78
2.0	31.55 ± 1.85	40.57 ± 5.93	25.34 ± 1.20	29.19 ± 0.73*
4.0	41.28 ± 3.31	53.49 ± 3.60*	38.90 ± 3.68	39.51 ± 1.74
6.0	48.37 ± 3.50	57.10 ± 1.81*	46.97 ± 2.02	48.89 ± 2.78
8.0	52.60 ± 2.64	56.00 ± 0.92*	49.06 ± 1.62	51.30 ± 1.44
12.0	49.51 ± 3.22	55.29 ± 1.07*	52.15 ± 2.07	50.66 ± 1.33
24.0	35.67 ± 2.14	50.91 ± 3.12*	49.58 ± 3.10	55.01 ± 1.66
30.0	31.78 ± 2.23	40.75 ± 3.99*	49.25 ± 4.33	57.63 ± 2.43
36.0	26.85 ± 1.50	32.42 ± 2.81*	47.21 ± 3.63	59.28 ± 2.27*
42.0	14.80 ± 2.07	29.23 ± 2.39*	43.43 ± 3.29	56.79 ± 3.65*
48.0	07.12 ± 1.24	21.75 ± 1.76*	42.90 ± 2.81	59.11 ± 4.65*

*Statistically significant $P < 0.05$

Induction of Diabetes: Diabetes was induced in the rats by administering 150 mg/kg of alloxan intraperitoneally into the 24 hours fasted rats (Ghosh, 1975). Blood samples were collected after 24 hours and blood glucose levels were estimated. Albino rats which have shown more than 200 – 250 mg % blood glucose levels were considered as diabetic. Blood glucose levels were monitored for five days. From this it was confirmed that diabetes was induced in 24 hours and stabilised within five days. These animals were used for further studies.

Diabetic rats were fasted for 18 hours and were divided into two groups. First group was treated with tolbutamide (40 mg/kg orally) and second group with glibenclamide (40 μg/kg orally). Blood samples were drawn at above mentioned time intervals and glucose levels were estimated. Lansoprazole 60 mg/kg/day for seven days was given to all the animals of both groups. On the seventh day, 6 hours after lansoprazole treatment the animals were kept for fasting. On the eighth day lansoprazole was administered as usual. One hour after the lansoprazole, animals of first group were given tolbutamide (40 mg/kg) and second group glibenclamide (40 μg/kg). Blood samples were drawn at above-mentioned intervals and blood glucose levels were estimated. Percentage blood glucose levels were calculated and presented in Table 2.

Statistical Analysis: The data were analysed by using Students' t-test. P values lower than 0.05 were considered as statistically significant.

Table 2. Effect of lansoprazole on the antidiabetic effect of tolbutamide and glibenclamide in diabetic rats.

Time in hrs.	% blood glucose reduction by tolbutamide before and after lansoprazole treatment (60 mg/kg)		% blood glucose reduction by glibenclamide before and after lansoprazole treatment (60 mg/kg)	
	Before	**After**	**Before**	**After**
Fasting	- - -	- - -	- - -	- - -
0.5	03.57 ± 0.95	02.57 ± 0.47	06.21 ± 0.49	01.68 ± 0.18
1.0	16.09 ± 4.96	11.60 ± 2.44	13.73 ± 0.94	12.81 ± 1.40
2.0	47.70 ± 7.18	48.77 ± 7.34	39.47 ± 4.63	36.23 ± 5.35
4.0	60.86 ± 8.53	75.78 ± 2.09	54.01 ± 5.01	52.89 ± 6.93
6.0	63.28 ± 7.40	80.01 ± 2.36	62.82 ± 3.74	69.75 ± 2.91
8.0	72.17 ± 4.38	84.96 ± 1.68*	71.43 ± 3.24	77.16 ± 3.39
12.0	76.63 ± 3.58	86.86 ± 1.46*	78.94 ± 3.31	81.58 ± 1.75
24.0	81.25 ± 1.95	86.13 ± 1.71	82.96 ± 2.36	86.29 ± 1.58
30.0	78.94 ± 1.78	84.50 ± 3.56	80.09 ± 1.96	87.30 ± 1.43*
36.0	78.41 ± 1.20	81.95 ± 4.30	73.03 ± 1.46	87.14 ± 1.49*
42.0	76.09 ± 1.73	80.04 ± 4.15	76.24 ± 1.33	87.07 ± 2.14*
48.0	70.54 ± 2.10	78.91 ± 3.67	74.81 ± 1.53	86.32 ± 2.79*

*Statistically significant $P < 0.05$

Results and discussion

For the assessment of the potentiation of hypoglycaemia, onset of action, (time taken to reduce minimum of 20 % reduction in blood glucose levels), peak effect, duration of hypoglycaemia (duration in which minimum of 20% reduction in blood glucose levels are maintained) were considered. It is evident from the Table 1, that after the lansoprazole pretreatment, the parameters of tolbutamide induced hypoglycaemia are altered significantly i.e., peak effect was enhanced from 52.60 % ± 2.64 at 8 hours to 57.10 ±1.81 at 6 hours and there was a prolongation of duration from about 34 hours to about 46 hours, but onset of action was not altered significantly. In case of glibenclamide induced hypoglycaemia, lansoprazole enhanced the peak effect from 52.15 % ± 2.07 at 12 hours to 59.28 % ± 2.27 at 36 hours and influence on the duration of action could not be assessed (as duration of hypoglycaemia was more than 46 hours without the treatment with lansoprazole), but onset of action was not altered significantly. In diabetic animals the influence of lansoprazole on the effect of sulfonylureas could not be ascertained. However the % blood glucose reduction in the glibenclamide treated group enhanced to such an extent that 2 animals died and 2 more animals showed the signs of hypoglycaemia (recovered after glucose treatment). Sulfonylureas are normally metabolised by microsomal enzyme system especially cytochrome P 450 2B4 and cytochrome P 450 3A6 and other enzymes to hydroxy and then to carboxy metabolites (Parent *et al.,* 1992). There are contradictory reports regarding the proton pump inhibitors and their effect on cytochrome P 450

enzyme system. Proton pump inhibitors like omeprazole inhibit the cytochrome P 450 enzyme system (Oosterhuis and Jonkman, 1989). lansoprazole pretreatment could not influence the onset of sulfonylurea-induced hypoglycaemia significantly. However peak effect and duration of action was enhanced significantly. Therefore it can be concluded that Lansoprazole pretreatment may not be interfering with absorption of sulfonylureas but may retard their metabolism by inhibiting the enzymes responsible for their metabolism. Further studies are undertaken to establish the influence of lansoprazole pretreatment on the pharmacokinetic parameters of these sulfonylureas. From the present study it may be suggested that blood glucose levels should be monitored and dose and frequency of administration of sulfonylureas requires to be readjusted.

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