

**A STUDY ON THE DRUG-DRUG INTERACTION OF
PANTOPRAZOLE WITH GLIPIZIDE IN RABBITS.**

S. Babitha*, B. Ramesh, Jaideep Singh

Department of Pharmacology, Sree Siddaganga College of Pharmacy, B.H. Road, Tumkur-572102.

Corresponding author e-mail:*jai_deep21@yahoo.com

Summary

Both diabetes and gastric ulcer are common health hazards both in terms of morbidity and mortality. In the first part of this investigation, the influence of glipizide (50µg/kg) on the blood glucose levels of healthy albino rabbits was analysed. The results have indicated that glipizide could produce significant hypoglycaemia and peak effect was 39.3 ± 1.09 at 12th hour. To the same animals pantoprazole at two dose levels 5mg/kg and 10 mg/kg was administered for 1 week and on 8th day both the drugs (pantoprazole and glipizide) were administered. The blood samples were collected at regular intervals and blood glucose levels were estimated. Pretreatment of pantoprazole (5mg/kg) for 7 days has shown ($40.9 \% \pm 8.5$) reduction of (blood glucose level) BGL of glipizide and at high dose (10mg/kg) for 7 days exhibits the reduction of BGL of glipizide significantly from 39.3 ± 1.09 to 55.1 ± 3.03 . In conclusion, the percentage reduction of blood glucose at 24 hours was observed at higher level of 46.9 ± 2.3 indicates the increase in duration of action of glipizide. In conclusion, Pantoprazole has significant increase in the hypoglycemic action of glipizide.

Keywords: Diabetes, Ulcer, Pantoprazole, Drug-drug interaction.

Introduction

Diabetes is a chronic metabolic disorder characterized by a high blood glucose concentration-hyperglycemia caused by insulin deficiency, often combined with insulin resistance. Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis¹. Gastric ulcer is one more chronic disease which requires treatment with drugs for prolonged period of time with H₂ blockers like ranitidine, and proton pump inhibitors like lansoprazole, pantoprazole etc².

Co-existence of diabetes mellitus and ulcer is quite common in India and hence antiulcer and antidiabetic agents are frequently given together. In such cases, the combination of anti ulcer agents and oral hypoglycaemic agents are used, viz., H₂ blockers like ranitidine/famotidine and proton pump inhibitors like pantoprazole /lansoprazole are combined with sulfonylurea like glipizide. There are reports indicating that H₂ blocker like ranitidine has influenced the antidiabetic effect of sulfonylureas³. Hence in the present study, an attempt was made to study the effect of commonly used antiulcer drug pantoprazole on hypoglycaemic and antidiabetic effect of glipizide in healthy albino rabbits.

Material and Methods

Animals: Albino rats of either sex weighing between 150-260 grams were selected for the study.

Method for collection of blood sample and plasma:

Blood samples were collected from the marginal ear vein. The dilated marginal ear vein was punctured by means of sharp 26-gauge needle in the direction of venous blood flow. The blood was collected into 3ml narrow test tubes containing a pinch of anticoagulant powder, they were sealed with thin aluminium foil and were stored at 2-8°C⁴ and the plasma was obtained by centrifuging the blood sample collected for 10 minutes, decanting the supernatant fluid into the clean, dry test tubes.

Influence of pantoprazole on blood glucose levels in healthy albino rabbits:

Albino rabbits of either sex weighing between 1.5-2.0 kg were divided into 2 groups (Group I and II) of 5 animals each. The animals were fasted for 18 hours before commencing the experiment. Group I animals received pantoprazole 10mg/kg orally and group II animals received 2ml of distilled water orally, which serves as control group. The time of drug administration was noted for all the animals. The blood samples were collected at 0.0, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 hours after the administration of pantoprazole and distilled water, and analyzed for glucose levels by using GOD / POD⁵. The blood glucose levels were expressed as mg/ 100ml of blood.

Effect of pantoprazole treatment on the hypoglycaemic activity of glipizide in healthy albino rabbits :

Albino rabbits of either sex weighing between 1.5-2.0 kg were divided into 2 groups (Group I and II) of 5 animals each. They were fasted for 18 hours before commencing the experiment. In the first part of this experiment, animals in the group I and II received suspension of glipizide 50µg/kg, orally. The blood samples were collected at 0.0, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 hours after the administration and analyzed for glucose levels by using GOD / POD⁵.

In the next part of this experiment, both two groups received solutions of pantoprazole 5mg/kg and 10mg/kg respectively for one week. On the 7th day, 6 hours after administration of pantoprazole the rabbits were fasted for 18 hours. On the 8th day, '0' hour blood samples were collected. Pantoprazole 5mg/kg and 10mg/kg was administered orally to groups I and II respectively. 60 minutes later glipizide 50µg/kg was administered to both the groups. Blood samples were collected thereafter at different time intervals up to 24 hours. Blood glucose was estimated by GOD/POD⁵.

Results

Influence of pantoprazole on blood glucose levels in healthy albino rabbits: Results presented in table no. 1 revealed that the Pantoprazole administration 10mg/kg has failed to influence the blood glucose levels in healthy albino rabbits significantly.

Effect of pantoprazole treatment on the hypoglycaemic activity of glipizide in healthy albino rabbits: As evidenced from experimental results presented in table no. 2 and 3 Glipizide (50 g/kg, oral) reduced the blood glucose levels to the extent of 39.3±1.09 (peak effect) at 12th hour and the onset of action (time taken to reduce the blood glucose levels to the extent of 15%) was about 2 hours. The duration of action was more than 22 hours. Pretreatment of pantoprazole (5mg/kg) for 7 days has shown 40.9 % ± 8.5 reduction of blood glucose level of glipizide. Where as the higher dose of pantoprazole (10mg/kg) Pretreatment for 7 days exhibits the reduction of blood glucose level of glipizide significantly from 39.3±1.09 to 55.1±3.03. The percentage reduction of blood glucose at 24 hours was observed at higher level of 46.9±2.3 indicates the increase in duration of action of glipizide.

Table-1: DATA SHOWING THE BLOOD GLUCOSE LEVELS AFTER THE ADMINISTRATION OF PANTOPRAZOLE (10mg /Kg) IN HEALTHY ALBINO RABBITS

Time In Hours	Blood Glucose Levels In mg % After Pantoprazole Administration #	Percentage Blood Glucose Reduction After Pantoprazole Administration #	Blood Glucose Levels In mg % # (Control Group)	Percentage Blood Glucose Reduction # (Control Group)
Fasting	90.0±4.5	-	90.1±4.1	-
1.0	90.7±8.2	-0.3±4.5	90.4±7.3	0.07±4.1
2.0	95.2±5.5	-5.6±2.4	94.2±5.6	-4.4±2.7
3.0	96.1±6.7	-6.5±2.8	93.0±3.0	-3.4±2.8
4.0	99.7±7.9	-10.3±3.4	97.4±6.7	-7.9±3.7
6.0	102.4±7.1	-13.5±4.0	98.9±7.0	-10.3±3.1
8.0	101.0±5.5	-12.1±3.2	98.3±5.2	-9.1±3.8
12.0	100.5±3.2	-11.8±2.4	98.2±3.3	-9.1±2.1
18.0	98.4±9.6	-8.8±5.8	95.8±7.0	-6.1±3.8
24.0	91.5±6.2	-1.6±5.3	91.7±5.1	-1.7±4.1

Values are mean ± SEM, *P<0.05, n=5, n=number of rabbits per group

Table-2: DATA SHOWING THE BLOOD GLUCOSE LEVELS WITH GLIPIZIDE (50µg/kg) IN HEALTHY ALBINO RABBITS BEFORE AND AFTER PANTOPRAZOLE (5mg/kg) TREATMENT

TIME IN HOURS	Blood Glucose levels In mg% Before Pantoprazole Treatment [#]	Blood Glucose levels In mg % After Pantoprazole Treatment [#]	Percentage Blood Glucose Reduction Before Pantoprazole Treatment [#]	Percentage Blood Glucose Reduction After Pantoprazole Treatment [#]
Fasting	142.6±16.4	133.7±4.0	-	-
0.5	145.7±25.6	122.8±3.7	0.42±6.3	6.9±1.0
1.0	139.4±26.0	108.7±5.8	3.5±6.9	18.9±3.2
2.0	113.1±13.4	100.7±9.6	20.3±5.2	24.5±7.5
3.0	115.5±13.7	99.4±9.0	18.6±3.7	25.3±8.2
4.0	108.8±13.8	98.0±8.2	23.3±5.5	26.3±7.4
6.0	101.8±13.6	99.8±6.9	28.3±5.3	25.4±4.6
8.0	98.4±6.8	90.1±6.3	29.7±4.9	32.0±6.6
12.0	99.8±5.7	78.3±9.2	28.3±7.1	40.9±8.5
18.0	112.5±6.8	83.8±8.4	19.1±8.0	36.7±8.0
24.0	123.6±8.3	91.5±8.8	11.0±9.8	31.0±8.4

Values are mean ± SEM, *P<0.05, n=5, n=number of rabbits per group

Table-3: DATA SHOWING THE BLOOD GLUCOSE LEVELS WITH GLIPIZIDE (50µg/kg) IN HEALTHY ALBINO RABBITS BEFORE AND AFTER PANTOPRAZOLE (10mg/kg) TREATMENT

TIME IN HOURS	Blood Glucose levels In mg% Before Pantoprazole Treatment [#]	Blood Glucose levels In mg % After Pantoprazole Treatment [#]	Percentage Blood Glucose Reduction Before Pantoprazole Treatment [#]	Percentage Blood Glucose Reduction After Pantoprazole Treatment [#]
Fasting	153.6±14.1	115.8±4.1	-	-
1.0	147.3±16.1	101.2±0.5	4.4±1.9	12.4±3.0
2.0	124.4±8.8	80.7±2.5	18.6±1.8	30.2±0.6*
3.0	115.8±8.5	72.2±5.8	24.3±1.4	37.8±3.1*
4.0	110.2±8.4	64.8±6.0	28.0±1.2	44.2±3.2*
6.0	96.9±9.3	57.8±2.1	36.8±2.3	50.0±0.6*
8.0	94.7±9.7	53.7±3.2	38.3±2.4	53.6±1.7*
12.0	92.9±7.0	51.8±3.7	39.3±1.0	55.1±3.0*
18.0	98.2±7.3	55.7±0.4	37.1±1.0	47.3±1.5*
24.0	110.4±6.9	61.4±3.8	28.6±2.7	46.9±2.3*

Values are mean ± SEM, *P<0.05, n=5, n=number of rabbits per group

Discussion

Diabetes mellitus is one of the chronic disorders, which requires treatment for prolonged period/life time. There are mainly two types of diabetes. In case of type 1 diabetes, β-cells of pancreas are destroyed completely and insulin synthesis is completely stopped. Hence such patients are to be treated with insulin. Type 2 diabetes accounts for 90% of the patient and the prevalence of diagnosed ratio is about 10% of the population⁶. Glipizide is one of the very important and popularly used sulfonylureas in controlling type 2 diabetes. Gastric ulcer is one more chronic disease which requires treatment with drugs for prolonged period of time⁷.

In the first phase of this investigation, an attempt was made to analyze the influence of glipizide (50µg/kg) on the blood glucose levels of healthy albino rabbits. The results have indicated that glipizide could produce significant hypoglycaemia and peak effect was 39.3±1.09 at 12th hour and the duration action was more than 22 hours.

To the same animals pantoprazole at two dose levels 5mg/kg and 10 mg/kg was administered for 1 week and on 8th day both the drugs (pantoprazole and glipizide) were administered. The blood samples were collected at regular intervals and blood glucose levels were estimated to assess the drug-drug interaction between them. Higher dose of pantoprazole (10mg/kg) increased the peak effect and duration of action of glipizide significantly.

The sulfonylureas are metabolized in the liver by microsomal enzyme-system¹. The increase in the percentage blood glucose reduction of glipizide by pantoprazole 10mg/kg pretreatment may be due to the enzyme inhibition. However this can be proved only after pharmacokinetic studies.

The present study suggests that, simultaneous treatment of peptic ulcer and diabetes mellitus with Pantoprazole and glipizide, the dose and frequency of administration of glipizide is to be readjusted accordingly, so as to avoid severe hypoglycemia.

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