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Original Article

EFFECT OF RANITIDINE ON HYPOGLYCAEMIC ACTIVITY OF GLIPIZIDE IN RABBITS

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ABSTRACT

Objective: To study the effect of Ranitidine (H_2 receptor antagonist) in combination with Glipizide on the blood sugar level in rabbits.

Methods*:* Six albino rabbits were taken for the study. Glipizide was administrated to each rabbit as a single drug therapy on day 1, while was co-administrated with Ranitidine to each rabbit as a combinational drug therapy on day 7. Ranitidine was administrated to each rabbit from day 2 to day 6 as a single drug therapy. Blood sugar levels were estimated on day 1 and on day 7 at 0, 1, 2, 4, and 6 h.

Results*:* The mean blood sugar level readings at 0, 1, 2, 4 and 6 h on day 1 were 90.9, 78.4, 67.2, 60.2 and 67.5 mg% and on day 7 were 90.3, 77.09, 63.3, 55.7 and 64 mg% respectively. When mean blood sugar level on day 1 and day 7 were considered, there was a significant reduction in blood sugar level at 2, 4 and 6 h but there was no significant fall in blood sugar level at 0 and 1 hour after co-administration of Glipizide and Ranitidine.

Conclusion: Ranitidine, when co-administered with glipizide, significantly increases the hypoglycaemic action of glipizide.

Keywords: Ranitidine, Glipizide, Hypoglycaemic, Blood sugar

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INTRODUCTION

Multiple drug therapy is common in type 2 diabetes mellitus treatment. Sulphonylurea or biguanides are two groups of drugs which are used for the treatment of type 2 diabetes mellitus. The simultaneous use of H_2 antagonist with sulphonylurea has been reported in type-2 diabetic patient also suffering from gastric ulcer [1]. Therefore, in such condition use of several drugs is often essential to obtain a desired therapeutic effect or to treat coexisting diseases.

Drug-drug interaction is one of the causes of adverse drug reactions. Generally, drug-drug interaction is common in multidrug therapy. Diabetic patients, particularly due to associated comorbidities, tend to have various drug-drug interactions due to the effect of multiple drugs [2].

Glipizide is a second-generation sulfonylurea antidiabetic drug. It is principally metabolized to inactive metabolites by genetically polymorphic CYP2C9 enzyme [3].

Glipizide is effective in lowering of blood glucose, well-tolerated as well as safe during long-term treatment. Glipizide is the agent characterized by rapid pharmacological action. It is indicated both in monotherapy and combined treatment with insulin or biguanides [4].

Drug interactions with the sulphonylurea group of oral hypoglycaemics may have important therapeutic consequences, as hypoglycaemia carries considerable morbidity and mortality. We therefore examined the interaction between ranitidine (H2-receptor antagonists) and glipizide as the latter agent is exclusively metabolised in the liver [5].

The objective of this study is to investigate the effect of ranitidine, a commonly used histamine H2-receptor antagonist, on the hypoglycemic activity of glipizide, a sulfonylurea medication, in rabbits.

MATERIALS AND METHODS

The study was carried out in the experimental room of the central animal house of Government Medical College, Aurangabad. Six healthy albino rabbits of either sex, weighing between 1.6 and 2.1 kg were used in the study. The study was approved by Institutional Animal Ethics Committee, Government Medical College, Aurangabad.

After getting approval from Institutional Animal Ethics Committee, the study was conducted under the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Rabbits were kept for fasting overnight for 18 h. Water was given *at libitum* and rabbits were kept at temp between 30-33 °C. For oral feeding rabbits, a special rabbit holding box and mouth gag with a feeding tube was used. During 7 d of study period, each rabbit was given Glipizide and Ranitidine as single-drug therapy and also as combination therapy, as shown below.

Day 1: Glipizide

Day 2-6: Ranitidine

Day 7: Glipizide+Ranitidine

All the drugs were suspended in 2% gum acacia and then administered. Doses of the drugs were calculated from Fundamental of experimental pharmacology [6]. About 1 ml of blood was collected from marginal ear vein of the rabbits for blood glucose estimation on day 1 and on day 7 at 0, 1, 2, 4, and 6 h. Blood sugar levels were estimated by modified Somogy's method [7] and expressed as milligram per 100 ml (mg %).

Statistical analysis

Mean blood sugar levels were expressed as milligram per 100 ml±SD (mg %±SD). The Student's t-test was used to test the significance of the difference between treated groups for the blood sugar level on day 1 and day 7 at 0, 1, 2, 4 and 6 h in each treated group and taken as significant at $p<0.05$.

RESULTS

The mean blood sugar level readings at 0, 1, 2, 4 and 6 h on day 1 were 90.9, 78.4, 67.2, 60.2 and 67.5 mg % and on day 7 were 90.3, 77.09, 63.3, 55.7 and 64 mg% after administration of Glipizide+Ranitidine respectively. When mean blood sugar level on day 1 and day 7 were considered, there was a significant reduction in blood sugar level at 2, 4 and 6 h, but there was no significant fall in blood sugar level at 0 and 1 h after co-administration of Glipizide and Ranitidine.

Table 1: Effect of ranitidine on hypoglycaemic activity of glipizide in rabbits

Drug	Mean blood sugar level (mg %±SD)				
	0 h	1 h	2 h	4 h	6 h
Glipizide (Day 1, n = 6)	90.9±1.49	78.4±1.49	67.2±0.65	60.2±2.48	67.5±1.01
Glipizide+Ranitidine (Day 7, n = 6)	90.3±1.74	77.0±1.33	63.3±0.71	55.7±0.79	64.0±0.67
P-value	>0.05	<0.05	<0.001	<0.01	<0.001

Value were expressed in mean±SD, Significant at P<0.05

DISCUSSION

This study demonstrates that there was a significant drop in blood sugar levels at 1, 2, 4, and 6 h following the administration of ranitidine along with glipizide. This may be the result of a drug-drug interaction between ranitidine and glipizide.

An important effect on blood sugar level was observed by Feely *et al.* (1993) [8] when glipizide was co-administered with H2 receptor antagonist like cimetidine and ranitidine. Their study has shown that administration of H2 antagonist cimetidine and ranitidine produces a marked reduction in blood sugar level in diabetic patients receiving glipizide and suggested the possible cause as the inhibition of glipizide metabolism by H2 antagonist.

As sulphonylureas are well known to be metabolized by liver microsomal enzyme system [5], the decrease in blood sugar level in combination with sulphonylureas is possible due to an effect of H2 receptor antagonist on hepatic metabolism.

Several interactions between ranitidine and some drugs like warfarin, metoprolol, nifedipine, theophylline, fentanyl have been established, which may be attributed to an effect of ranitidine on hepatic metabolism [9].

As glipizide is completely absorbed and metabolised extensively in the liver [5, 8] it is possible that the increased glipizide concentrations are due to an effect of the H2-receptor antagonist on hepatic metabolism.

The interaction between ranitidine and glipizide is an important consideration, especially for patients with diabetes who are taking glipizide to manage their blood sugar levels.

Ranitidine is a histamine H2 receptor antagonist commonly used to reduce stomach acid production, often prescribed to treat conditions like peptic ulcers, gastroesophageal reflux disease (GERD), and gastritis. Glipizide, on the other hand, is an oral antidiabetic medication belonging to the sulfonylurea class, which stimulates the release of insulin from the pancreas to lower blood sugar levels.

The concern with the combination of ranitidine and glipizide lies in the potential for ranitidine to inhibit the metabolism of glipizide, leading to an increase in its blood levels and prolonged hypoglycemic effects, which may be because ranitidine can inhibit the cytochrome P450 enzyme system, particularly the CYP2C9 isoenzyme, which is responsible for the metabolism of glipizide.

As a result, when ranitidine is co-administered with glipizide, the clearance of glipizide from the body may be reduced, leading to higher plasma concentrations of glipizide and an increased risk of hypoglycemia.

Healthcare providers should be cautious when prescribing ranitidine to patients taking glipizide, especially those who are elderly or have impaired hepatic function, as they may be more susceptible to the effects of hypoglycemia.

In the present study at 0 h, there was no significant change in blood sugar level, which clearly indicates that ranitidine by itself exerts no effect on blood sugar level or they do not have hypoglycemic activity.

CONCLUSION

Ranitidine, when co-administered with Glipizide significantly enhances hypoglycaemic action of Glipizide. Therefore, co-administration of Glipizide with Ranitidine needs to be carefully monitored in diabetic patients, as glucose control may be lost due to drug-drug interaction.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

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