

Original article

Comparative Effects of Cimetidine on Hypoglycaemic Activity of Glibenclamide in Rabbits

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Abstract:

Background: Multiple drug therapy is common in Type 2 diabetes mellitus treatment. Aim and Objectives: To study the effect of Cimetidine (H₂ antagonist) in combination with Glibenclamide on the blood sugar level in rabbits. The objectives of present study were to check drug-drug interaction for avoiding multi-drug therapy in diabetes.

Material and Methods: Six albino rabbits were taken for the study. Glibenclamide was administered to each rabbit as a single drug therapy on day 1 while was co-administered with Cimetidine to each rabbit as a combinational drug therapy on day 7. Cimetidine was administered 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 hours.

Results: When compared on day 1 and day 7, no significant reduction was observed in blood sugar level at 0 hour. The reduction of blood sugar levels at 1 and 2 hours were extremely significant ($P < 0.001$) while highly significant at 4 and 6 hours after co-administration of Glibenclamide and Cimetidine.

Conclusion: Cimetidine when co-administered with glibenclamide significantly increases the hypoglycaemic action of glibenclamide.

Keywords: Cimetidine, Glibenclamide, Hypoglycaemic

Introduction:

Multiple drug therapy is common in Type 2 diabetes mellitus treatment. Sulphonylurea or biguanides are two groups of drugs, which are used for treatment of type-2 diabetes mellitus. The simultaneous use of H₂ 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 the coexisting diseases.

Cimetidine is well known to interact with a number of drugs concurrently administered by inhibiting hepatic microsomal enzymes [2]. Adverse effects due to interaction of Cimetidine with Warfarin [3], Phenytoin [4], Theophylline [5], Propranolol [6] have been reported. Drug interaction with sulphonylurea group of oral hypoglycaemic agents may have important therapeutic consequences as hypoglycaemia

carries considerable morbidity and mortality. Therefore, it was thought necessary to compare the effects of Cimetidine in the presence of sulphonylurea.

Material 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. Experiment study was conducted with the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) for animal experimentation of laboratory and the study was approved by Institutional Animal Ethics Committee, Government Medical College, Aurangabad.

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

Day 1: Glibenclamide

Day 2-6: Cimetidine

Day 7: Glibenclamide + Cimetidine

All the drugs were suspended in 2% gum acacia and then administered. Doses of all the drugs were calculated from experimental pharmacology [7]. About 1ml 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 hours. Blood sugar levels were estimated by modified Somogy's method [8] with help of Kleitt-Summerson colorimeter.

Results:

The mean blood sugar reading at 0, 1, 2, 4 and 6 hours on day 1 were 91.6, 81.7, 73.1, 60.6 and 65.9 mg % after administration of glibenclamide and on day 7 were 91.1, 76.5, 62.1, 55.6 and 62.2 mg % after administration of Glibenclamide + Cimetidine respectively. When blood sugar readings on day 1 and day 7 were compared, there was no significant reduction in blood sugar level at 0 hour, but at all 1, 2, 4 and 6 hrs the blood sugar levels were significantly reduced after administration of Glibenclamide + Cimetidine.

Table 1: Effect of Cimetidine on Hypoglycaemic Activity of Glibenclamide in Rabbits

Drug	Blood sugar level (mg %)				
	0 hr	1 hr	2 hr	4 hr	6 hr
Glibenclamide (Day 1) (n=6)	91.6 ±	81.7 ±	73.1 ±	60.8 ±	65.9 ±
Glibenclamide + Cimetidine (Day 7) (n=6)	91.1 ±	76.5 ±	62.1 ±	55.6 ±	62.2 ±
P- value	>0.05	<0.001	<0.001	<0.05	<0.01
<i>Values were expressed in Mean ± SEM , Significant at P<0.05</i>					

Discussion

Many studies have revealed the existence of number of drug interactions involving the inhibition of hepatic microsomal drug metabolism by drugs containing aromatic nitrogenous basis such as imidazole structure [2]. An important effect on blood sugar level was observed by Feely *et al.* (1993) [9] 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 [10], the decrease in blood sugar level in combination with sulphonylureas is possible due to an effect of H₂ receptor antagonist on hepatic metabolism. Cimetidine an imidazole derivative has high binding affinity for cytochrome P450 enzymes [11] and thus decreases the hepatic microsomal drug metabolism which is responsible for prolong action of the drug co-administered along with cimetidine.

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

Conclusion

Cimetidine when co-administered with glibenclamide significantly enhances hypoglycaemic action of glibenclamide. Therefore, combination of glibenclamide with Cimetidine would have to be carefully monitored in diabetic patients, as delicate glucose control may be lost due to drug interaction.

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