Acta Pharmaceutica Turcica
XLII (4) (135-138) 2000

INFLUENCE OF OMEPRAZOLE ON HYPOGLYCAEMIC ACTIVITY OF GLIBENCLAMIDE AND TOLBUTAMIDE IN NORMAL ALBINO RABBITS

VIKAS KUMAR*, N. VENKAT RAO, S. RAMACHANDRA SETTY**

Department of Pharmacology, V.L. College of Pharmacy,
Raichur-584 101, Karnataka, India.

The influence of omeprazole on hypoglycaemic activity of glibenclamide and tolbutamide was studied in albino rabbits. Omeprazole (30 and 60 mg/kg, po for seven consecutive days), glibenclamide (40 μg/kg, po) and tolbutamide (40 mg/kg, po) were suspended in 5% gum acacia in distilled water. Control rabbits were treated with 5% gum acacia suspension in distilled water. Animals were fasted for 18 hours before commencing experiments and blood samples were withdrawn by puncturing the marginal ear vein for measuring initial blood glucose concentration. After administration of the drugs the blood samples were withdrawn later at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18 and 24 proceeding hours and analysed for blood glucose levels by using UV spectrophotometer at 540 nm. Omeprazole treatments (30 and 60 mg/kg, po, for one week) significantly enhanced the hypoglycaemic activity of glibenclamide (40 μg/kg, po) and exhibited no significant change in the hypoglycaemic activity of tolbutamide (40 mg/kg, po) when compared to the control group. The present study indicates that the dose and/or frequency of glibenclamide has to be readjusted accordingly while using glibenclamide and omeprazole concomitantl

Keywords: *Omeprazole; Glibenclamide; Tolbutamide; Hypoglycaemic activity; Interaction.*

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentration known as hyperglycaemia, and it warrants careful management by the administration of drugs coupled with diet control and exercise. It may occur either due to decreased synthesis in insulin (type – I diabetes) or due to defective insulin secretion from β cells of Langerhans islets of pancreas (type – II diabetes). Insulin is used in treating type – I diabetes whereas sulphonylureas are the drugs of choice in type – II. Chronic diabetes are more liable to develop multiple pathology. Reports on diabetic patients do reveal that the incidence of fungal infections, cardiovascular disorders, nephropathy, retinopathy, neuropathy, sexual impotence, hyperacidity and respiratory tract infections are quite high in diabetics. Thus there in every possibility of administering other drugs along with sulphonylureas in treating type – II diabetes and this may create drug interaction problem. In fact recent studies revealed pharmacokinetic

*Present address: Pharmacology Laboratory, Department of Pharmaceutics, Institute of Technology, Banaras Hindu university, Varanasi-221 005, U.P., India
**Correspondent author E-mail : vkarya1973@yahoo.com

interaction between tolbutamide and ketaconozole in rabbits(1, 2), humans(3) and with ranitidine in rabbits(4). The simultaneous use of ranitidine with sulphonylureas in type–II diabetic patients, also suffering from gastric ulcers is quite common(5). A case report indicate that ranitidine enhanced the hypoglycaemic activity of glibenclamide in a diabetic patient also suffering from erosive esophagitis(6). Inspite of this, tight control of blood glucose levels in diabetics on drug therapy is essential and there may be occasion of polypharmacy with both classes of drugs for the treatment of diabetes and peptic ulcer simultaneously. Keeping this in mind, we lanned to investigate the influence of omeprazole, a recently introduced drug from proton-pump inhibitor and widely used in the treatment of peptic ulcer, on the hypoglycaemic activity of glibenclamide and tolbutamide in normal albino rabbits.

Materials and Methods

Animals

The study was conducted on albino rabbits (1.5 – 2.0 kg) which of either sex, were procured from the Central Animal House, V.L. College of Pharmacy. They were randomly distributed into different experimental groups and were acclimatized for at least one week in animal house before use. The animals were kept in colony cages (2 rabbits/cage) at ambient temperature of 25° ± 2°C and 4.5 – 5.5% relative humidity, with a 12 hr light/12 hr dark cycle. Each group consisted of five animals.

Drug treatments

Omeprazole (30 and 60 mg/kg, po for seven consecutive days), glibenclamide (40 (µg/kg, po) and tolbutamide (40 mg/kg, po) were suspended separately in 5% gum acacia in distilled water. Control rabbits were treated with 5% gum acacia suspension in distilled water. Omeprazole was obtained from M/s Dr. Reddy's Laboratories Ltd., Hyderabad, whereas glibenclamide and tolbutamide were obtained from M/s Hoechst (India) Ltd., Mumbai. Other chemicals used were of analytical reagent (AR) grade. Animals were fasted for 18 hours with water *ad libitum* before commencing experiments and blood samples were withdrawn for measuring initial blood glucose concentration by puncturing the marginal ear vein. After drugs administration, blood samples were withdrawn later at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18 and 24 hours and stored in refrigerator until analysis.

Determination of glucose in blood samples

The method of Nelson & Somogyi's was used(7). Briefly, blood samples were mixed with barium hydroxide followed by thorough mixing with zinc sulphate, filtered and the protein free filtrate was transferred to Folin-WU tubes. Alkaline copper sulphate reagent was added to all tubes and then heated in a boiling water bath for 20 minutes. Tubes were then cooled in running tap water, arsenomolybdate colour reagent was added and mixed gently without shaking. The volume of the solution was made upto 12.5 ml with distilled water and the optical densities were measured at 540 nm by using UV spectrophotometer (Shimadzu, Japan). The blood glucose concentrations were estimated from the calibration curve and were expressed as mg/100 ml of blood.

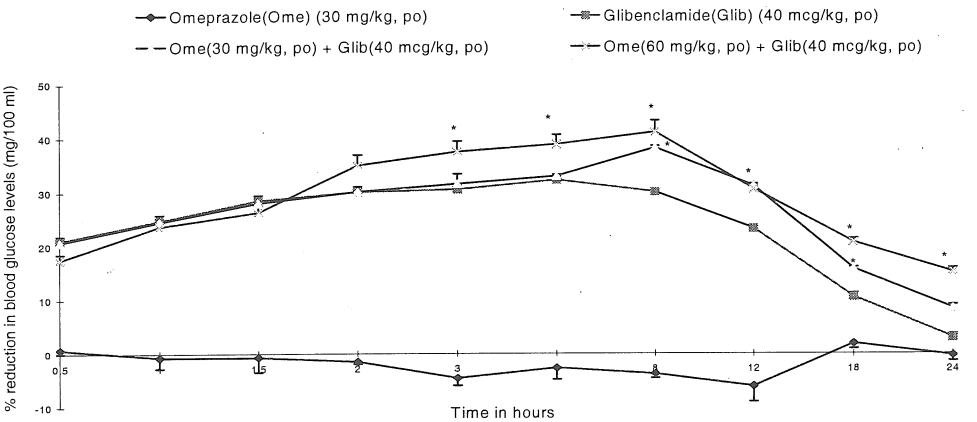
Statistical analysis

The data were analysed by using the one way ANOVA followed by Student's-*t* test (paired). *P* values lower than 0.05 were considered as statistically significant.

Results and Discussion

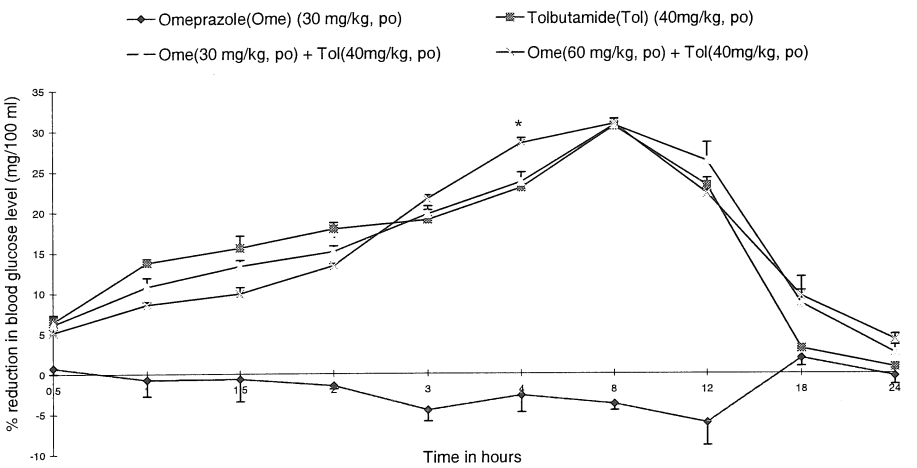
The mean per cent blood glucose reduction by glibenclamide and tolbutamide before and after treatment with omeprazole and omeprazole alone are shown in Figs. 1 and 2 respectively. With omeprazole treatment, hypoglycaemic activity of tolbutamide was not altered significantly, however, omeprazole treatment significantly

enhanced the hypoglycaemic activity of glibenclamide in rabbits when compared with control group. Inspite of this, omeprazole also increased the duration and peak effect of glibenclamide (Fig. 2).



* indicate statistical significance at $p<0.05$.

Fig. 1. Indicate of omeprazole on hypoglycaemic activity of glibenclamide



* indicate statistical significance at $p<0.05$.

Fig. 2. Influece of omeprazole on hypoglycaemic activity of tolbutamide

The drug interaction studies are usually conducted in animal models to find out the mechanism before they are conducted in humans. We used rabbit as the animal model since it is one of the animals for bioassay of insulin, and can be maintained easily in laboratory conditions and required number of blood samples can easily be collected at the desired time intervals.

In clinical practice sulphonylureas are administered orally. Hence in our study also they were administered orally as gum acacia suspension. Glibenclamide and tolbutamide are metabolised (oxidised) by hepatic microsomal

enzyme cytochrome P 450 2B4 and cytochrome P 450 3A6 and by other enzymes to hydroxy and then to carboxy metabolites(8). The hydroxy metabolite is the major one in rabbits and rats(9) and the carboxy metabolite is the major one in humans(10). It is a known fact that the multidrug therapy in many cases cause interactions among the drugs leading either increase or decrease and/or nullify the effect of drug. Some drugs may induce or inhibit the microsomal enzymes of the liver and thereby increase or reduce the metabolism of drug to shorten or lengthen their duration of action. Omeprazole might be affecting through microsomal enzymes as it has potentiated the hypoglycaemic activity of glibenclamide.

With glibenclamide, a significant reduction in blood glucose levels was seen at 0.5 hr. The pretreatment with omeprazole (30 & 60 mg/kg, po for seven days) has not altered the onset of action of glibenclamide but duration of action was enhanced to the extent of 3 and 9 hrs with omeprazole 30 and 60 mg/kg, po dose respectively. In addition, the peak effect of glibenclamide was also increased significantly by omeprazole. All these observations indicate that the dose, frequency or both of glibenclamide has to be readjusted accordingly while using glibenclamide and omeprazole concomitantly. The glibenclamide interaction study was conducted with single dose treatment (acute). The effect of multiple dose treatment in normal rabbits and later in diabetic rabbits followed by clinical trials need to be conducted to find the clinical significance of this drug combination. Lastly, these findings also need to be confirmed by studying the pharmacokinetic parameters of glibenclamide with omeprazole combination.

Acknowledgements

We express our sincere thanks to M/s Dr. Reddy's Laboratories Ltd., Hyderabad and M/s Hoechst (India) Ltd., Mumbai for kindly supplying us gift samples of drugs. Thanks are also due to Prof. S.M. Shanta Kumar and Prof. M.B. Raju, V.L. College of Pharmacy Raichur, for helpful discussions.

References

1. Krishnaiah, Y.S.R., Satyanarayana, S., Visweswaram, D.: Indian J. Pharm. Sci.: 54, 88 (1994)
2. Krishnaiah, Y.S.R., Satyanarayana, S., Visweswaram, D.: Indian J. Pharmacol. 25, 146 (1993)
3. Krishnaiah, Y.S.R., Satyanarayana, S., Visweswaram, D.: Br. J. Clin. Pharmacol. 37, 205 (1994)
4. Krishnaiah, Y.S.R., Satyanarayana, S., Visweswaram, D.: Indian J. Physiol. Pharmacol. 39, 71 (1995)
5. Krishnaiah, Y.S.R., Satyanarayana, S., Visweswaram, D.: Indian J. Physiol. Pharmacol. 38(4) 316 (1994)
6. Lee, K., Mize, R., Lowenstein, S.R. : Ann. Intern. Med. 107, 261 (1987)
7. Nelson, E., Reilly, L.O., Chulski, T. : Clin. Chem. Acta. 5, 774 (1960)
8. Parent, C., Pierre, M., Jutras, B.L., Souich, P.D. : J. Pharmacol. Exp. Ther. 261, 1128 (1992)
9. Thomas, R.C., Ikeda, G.J. : J. Med. Chem. 9, 507 (1966)
10. Satyanarayan, S. : In thesis submitted to Andhra University for the award of Ph.D. 1984.

Accepted 04.04.2000