Indian J Physiol Pharmacol 1994; 38(4) : 316-318

INFLUENCE OF RANITIDINE ON THE HYPOGLYCAEMIC ACTIVITY OF GLIBENCLAMIDE AND TOLBUTAMIDE IN RABBITS

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(Received on July 23, 1993)

Abstract: The influence of ranitidine on the hypoglycaemic activity of glibenclamide and tolbutamide was studied in rabbits. Ranitidine treatment (15 mg/kg, po, twice daily for one week) enhanced the hypoglycaemic activity of glibenclamide (40 µg/kg, po) while it has not altered either the hypoglycaemic activity or pharmacokinetics of tolbutamide (40 mg/kg, po) in rabbits.

Key words: ranitidine, hypoglycaemic activity, glibenclamide, tolbutamide, pharmacokinetics, interaction

INTRODUCTION

The simultaneous use of ranitidine with sulphonylureas in type II diabetic patients also suffering from gastric ulcers is quite common. A case report indicated that ranitidine enhanced the hypoglycaemic activity of glibenclamide in a diabetic patient also suffering from erosive esophagitis (1). In another study, ranitidine was shown potentiating the hypoglycaemic action of glipizide in humans (2). It is planned to verify whether ranitidine causes a regular interaction with sulphonylureas or it was an accidental observation found with glibenclamide. In the present paper, a preliminary study on the influence of ranitidine on the hypoglycaemic activity of glibenclamide and tolbutamide in rabbits is reported.

METHODS

Experimental procedure: Albino rabbits of either sex weighing 1.2 to 2.1 kg were divided into four groups of five each. Group I and Group III were treated with aqueous solution of ranitidine hydrochloride (15 mg/kg, po, twice daily) for one week. Groups II and IV received only the vehicle for one week. All rabbits were fasted for 18 hours and blood samples were withdrawn (half an hour after the administration of last dose of either ranitidine or the vehicle) from the marginal ear vein for initial blood glucose estimation. Groups I and II were administered single dose (40 µg/kg, po) of glibenclamide (dissolved in minimum quantity of dilute alcohol). Groups III and IV were administered single dose (40 mg/kg, po) of tolbutamide (as a suspension in 5% gum acacia). Blood samples were withdrawn thereafter at different time intervals upto 24 hours and analysed for glucose (3) and/or tolbutamide (4). Absence of interference of ranitidine in the estimation of blood tolbutamide and glucose was confirmed with adequate recovery studies.

Data analysis: Concentration-time data of tolbutamide was analysed by nonlinear least squares method using the computer programme, MULTI (5). The parameters obtained thereby i.e., C_0, Kel and Ka

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were used in calculating other pharmacokinetic parameters. The terminal half-life ($t\frac{1}{2}$) was calculated using the relationship $t^1/_2 = 0.693/Kel$. Volume of distribution (V_d) was calculated using the relationship $V_d = F \times Dose/C_0$. The area under the blood tolbutamide vs time curve from 0 to 24 hours ($AUC_{0\rightarrow 24h}$) was calculated using the trapezoidal rule. The area under the blood tolbutamide vs time curve from 0 to ∞ hours ($AUC_{0\rightarrow\infty}$) was calculated by taking the sum of $AUC_{0\rightarrow 24h}$ and $C_{24\ h}/K_{el}$ (where C_{24h} is the blood tolbutamide concentration at 24 hours). The time required for maximum concentration (T_{max}) was calculated using the formula.

$$T_{max} = \frac{2.303}{(K_a - K_{el})} \times \log \frac{K_a}{K_{el}}$$

The maximum drug concentration attained (C_{max}) was calculated using the formula

$$C_{max} = \frac{F \times Dose}{V_d} \times e^{-K_{el} \times T_{max}}$$

Since sulphonylureas are absorbed completely after oral administration, F is taken as 1 (where F is the fraction of the dose absorbed).

The data are presented as mean ± SEM. The significance of the observed differences in the blood glucose concentrations and the pharmacokinetic parameters between the control and ranitidine treated groups of rabbits was assessed by Student's unpaired 't'-test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Ranitidine treatment did not affect any of the pharmacokinetic parameters of tolbutamide in rabbits when compared to control group (Table I). Also tolbutamide hypoglycaemic activity was not altered significantly in ranitidine treated rabbits. But ranitidine treatment significantly enhanced hypoglycaemic activity of glibenclamide in rabbits when compared to control group. An earlier and prolonged hypoglycaemic action of glibenclamide was also observed in ranitidine treated rabbits (Table II).

TABLE I: Influence of ranitidine on the pharmacokinetic parameters of tolbutamide in rabbits.

Parameter	*Control (n=5)*	*Ranitidine treated (n=5)*
Ka (h^{-1})	0.56 ± 0.06	0.65 ± 0.05
$AUC_0 -> \infty$ (μg. h/mL)	1265.8 ± 82.6	1267.7 ± 72.2
$T_{1/2}$ (h)	6.0 ± 0.3	5.8 ± 0.1
T_{max} (h)	3.7 ± 0.3	3.2 ± 0.1
C_{max} (μg/mL)	96.1 ± 5.8	108.5 ± 4.9
V_d (mL)	495.7 ± 50.8	499.6 ± 28.9

TABLE II: Influence of ranitidine on the hypoglycaemic activity of glibenclamide and tolbutamide in rabbits.

Time (hr)	Blood glucose concentrations (mg%) with			
	Glibenclamide		*Tolbutamide*	
	Control (n=5)	*Ranitidine treated (n=5)*	*Control (n=5)*	*Ranitidine treated (n=5)*
0	91.4 ± 3.0	99.8 ± 1.2	106.8 ± 8.9	97.8 ± 4.5
1	—	—	102.6 ± 9.2	87.4 ± 2.9
2	82.6 ± 1.6	58.2 ± 1.4*	83.0 ± 10.8	82.4 ± 2.5
3	—	—	83.2 ± 6.4	70.4 ± 3.5
4	97.4 ± 2.2	64.4 ± 1.7*	78.4 ± 5.2	64.8 ± 3.9
8	65.0 ± 2.3	70.4 ± 1.7	80.8 ± 7.5	71.0 ± 2.6
12	69.8 ± 3.8	78.4 ± 1.3	84.8 ± 8.9	79.8 ± 4.2
18	—	—	87.6 ± 9.2	88.0 ± 4.4
24	95.2 ± 5.7	79.4 ± 0.6*	105.6 ± 7.7	97.8 ± 5.0

*Significant at $P < 0.05$

DISCUSSION

The drug interaction of glibenclamide with ranitidine reported in a diabetic patient was also seen to occur in rabbit model. But the influence of ranitidine on blood glibenclamide concentrations is not known. Since tolbutamide is also another member of the oral antidiabetic drugs of sulphonylurea type, the study was also carried out to find the influence of ranitidine on blood tolbutamide concentrations and on its

hypoglycaemic activity in order to verify whether the same interaction occurs with this drug also. But neither the hypoglycaemic activity nor the pharmacokinetics of tolbutamide was significantly altered by ranitidine.

Controlled studies in normal subjects and patients have shown (6) that ranitidine did not affect the pharmacokinetics of several drugs including theophylline, diazepam, phenytoin, lidocaine, doxepin, amitriptyline, imipramine, meperidine, propranolol and tocainide (metabolised by liver). The unaltered pharmacokinetics of tolbutamide in our study also indicate the poor influence of ranitidine on hepatic microsomal enzyme activity and consequent alteration in drug metabolism since tolbutamide is mainly metabolised by the hepatic microsomal enzymes. Our earlier studies *in vivo* in rabbits using antipyrine as a marker drug also indicated the absence of ranitidine influence on hepatic drug metabolising activity (7). This might be due to the lower binding affinity of ranitidine for drug metabolising enzymes (8). Thus the results show that ranitidine-glibenclamide interaction involves a mechanism other than an alteration in hepatic drug metabolising activity.

ACKNOWLEDGEMENTS

Authors are thankful to the UGC for awarding a Research Fellowship to one and to M/s Cadila Laboratories, M/s Hoechst (India) Limited and M/s The Boots Company (India) Limited for the supply of gift samples of drugs.

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