EFFECT OF CLARITHROMYCIN ON THE PHARMACOKINETICS OF TOLBUTAMIDE

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SUMMARY

The aim of this 2x2 randomized double blind crossover study was to evaluate the effect of a single dose of clarithromycin on the pharmacokinetics of tolbutamide in nine healthy male volunteers. Each volunteer received orally 500 mg of tolbutamide, or 500 mg of tolbutamide and 250 mg of clarithromycin. The washout period between the two treatments was 7 days. Serum levels of tolbutamide were determined by HPLC. Serum profiles were analysed using a non-compartmental model. Blood glucose levels were also estimated using a glucometer (Ames) and Glucostix® (Bayer). There was ~20% increase in mean absorption rate constant and 26% increase in mean bioavailability of tolbutamide in the presence of clarithromycin. A hypoglycemic effect was reported upon co-administration of the two drugs.

KEY WORDS

pharmacokinetics, drug interaction, tolbutamide, clarithromycin

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INTRODUCTION

Clarithromycin, 6-O-methyl erythromycin A, has demonstrated excellent *in vitro* activity against both standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms. It is indicated for the treatment of upper and lower respiratory tract, skin and soft tissue infections, infections due to *Chlamydia*, mycoplasma and *Legiolenna*, and for the eradication of *H. pylori* in combination with acid suppressants. Clinical studies indicate that there is a statistically significant increase in the blood levels of some co-administered drugs, such as theophylline, fluoxetine, carbamazepine, digoxin, cyclosporin, warfarin, etc. /1-10/, which is due to its inhibitory effect on cytochrome P-450 enzymes.

The aim of the present study was to determine the effect of clarithromycin co-administration on the pharmacokinetics of tolbutamide, an oral hypoglycemic agent.

MATERIALS AND METHODS:

Chemicals

We used tolbutamide tablets 500 mg (Rastinon®; Hoechst Marion Rousell India Ltd., Mumbai, India), clarithromycin tablets, 250 mg (Crixan®, Crosslands, Mumbai, India), methanol HPLC (Ranbaxy Chemicals Ltd., India), and acetonitrile HPLC (Ranbaxy Chemicals Ltd., India). All other chemicals used were of AR grade.

Subjects

Nine healthy male volunteers aged 21-25 years, weighing 53-65 kg, participated in the study. All subjects underwent physical examinations and laboratory tests on blood and urine. All subjects were nonsmokers, had taken no medication for at least 14 days before entering the study, and were confined to the laboratory on study days.

This study was approved by the institutional ethics committee and written informed consent was obtained from the volunteers.

Protocol

The subjects were randomly divided into two groups and the study was conducted with a double blind crossover design with a wash-out period of 7 days. After fasting for 10-12 hours, volunteers were given 40 g glucose with 200 ml water at 7.30 a.m. Initial blood glucose was estimated at 8.00 a.m., followed immediately by oral administration of 500 mg of tolbutamide plus placebo or the combination of 500 mg of tolbutamide and 250 mg of clarithromycin with 200 ml water. No food or drink was permitted for 3 hours after drug administration and subjects remained sitting. Blood samples (3 ml) were withdrawn at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 14 and 24 h after drug administration. The samples were allowed to clot and serum was separated. Serum samples were frozen until assayed for tolbutamide concentration.

A second part of the study was conducted in the same volunteers for the estimation of blood glucose levels. The subjects were randomly divided into two groups. The study was conducted in double blind crossover fashion. The protocol was the same as that in the first part. The volunteers received either placebo or a clarithromycin tablet with the tolbutamide tablet. Blood was collected at 0, 1, 2, 3, 4 and 6 h after administration of the drugs. Blood glucose levels were estimated using a glucometer (Ames) and Glucostix® (Bayer).

Assay

Tolbutamide was analyzed in serum by HPLC using the modified method reported by Csillag *et al.* /11/. Chlorpropamide (internal standard) solution (0.1 ml; 0.01 mg/ml) was added to 0.5 ml of serum followed by 0.1 ml of 1 N HCl. The mixture was vortexed for 1 min. 5 ml of dichloromethane was added and the mixture mixed for 15 min followed by centrifugation at 3000 rpm for 10 min. The organic layer was separated and collected in a clean test tube. The dichloromethane was evaporated to dryness and the residue was reconstituted in 0.1 ml of mobile phase.

The chromatographic conditions were Spherisorb ODS-II column (125x4.6) with mobile phase acetonitrile:isopropanol:0.1%v/v ortho-phosphoric acid solution (17:17:66, v:v:v), detector wavelength 254 nm, and flow rate 1 ml/min.

Calculation of bioavailability data

Serum drug levels were used to calculate various pharmacokinetic parameters. The peak serum concentration (C_{max}) and the time to peak (T_{max}) were obtained from the experimental data. Other parameters, elimination half life ($t_{½}$), absorption rate constant (K_a), area under the serum concentration curve (AUC), volume of distribution (Vd/f) and systemic clearance (Cl/f) were calculated using noncompartmental methods.

The resulting means of the various pharmacokinetic parameters when tolbutamide was given alone or in combination of clarithromycin were compared using Student's t-test (paired data). A value of $p<0.05$ was considered statistically significant.

RESULTS

Mean serum concentrations of tolbutamide in the presence or absence of clarithromycin are shown in Figure 1. The various pharmacokinetic parameters of tolbutamide calculated from the serum concentrations are given in Table 1. Serum blood glucose levels over time in the presence or absence of clarithromycin are given in Figure 2 and Table 2.

All subjects tolerated the single dose of tolbutamide without any adverse effect, but when tolbutamide was co-administered with clarithromycin, seven of the nine volunteers complained of 'uneasiness' or giddiness (i.e., a hypoglycemic effect) in the first part of the study, and all nine volunteers in the second part. Significant changes in K_a, AUC, Cl/f and C_{max} were found in the presence of clarithromycin (Table 1).

From Figure 2, it appears that there was no clear effect of clarithromycin on mean blood glucose values after tolbutamide administration, but when we consider individual values (Table 2), a very rapid decline in blood glucose levels was observed in five volunteers in the presence of clarithromycin in the first hour after drug administration, while in the other four there was no significant change, even though all the volunteers complained of 'uneasiness' and giddiness when clarithromycin was co-administered.

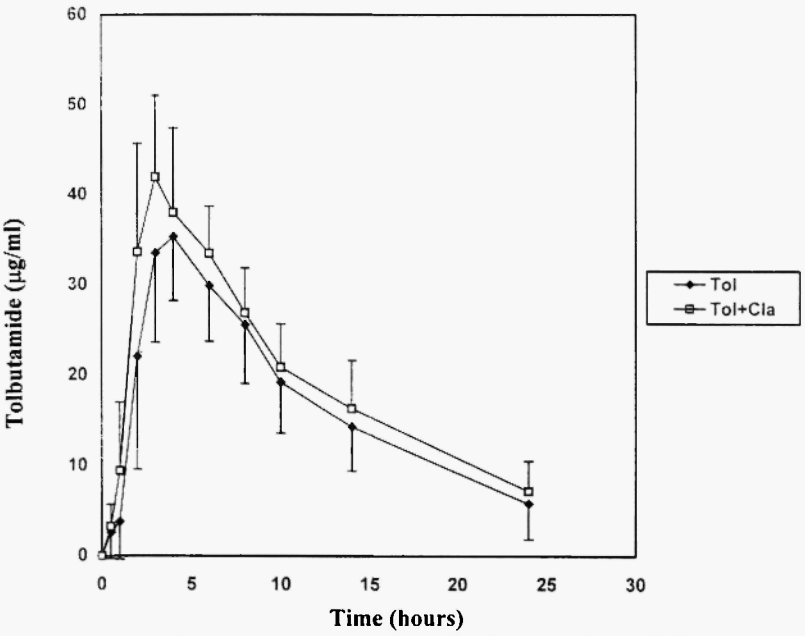

Fig. 1: Mean plasma levels of tolbutamide with and without clarithromycin co-administration.

TABLE 1

Various pharmacokinetic parameters of tolbutamide (500 mg) administered on its own or in combination with clarithromycin (250 mg)

Pharmacokinetic parameter		**Tolbutamide**	**Tolbutamide + clarithromycin**
$AUC_{0-\infty}$	(µg/ml/h)	431.89 ± 87.78*	543.31 ± 115.5*
$t_{½}$	(h)	8.19 ± 1.62	9.19 ± 2.39
K_a	(h^{-1})	1.54 ± 0.24	1.83 ± 0.56*
Vd/f	(l)	14.01 ± 3.16	12.54 ± 2.32*
Cl/f	(l/h)	1.19 ± 0.23	0.93 ± 0.21*
C_{max}	(µg/ml)	39.43 ± 5.71	46.84 ± 5.9*
T_{max}	(h)	3.22 ± 0.66	3.5 ± 1.06

* Significant at $p<0.05$

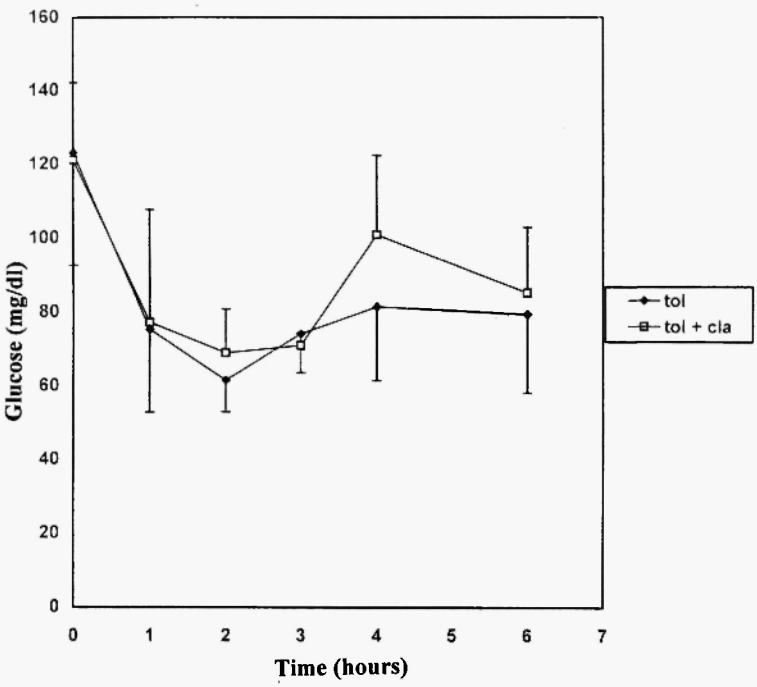

Fig. 2: Mean blood glucose levels after administration of tolbutamide with and without clarithromycin co-administration.

DISCUSSION

There was an increase in the mean C_{max} values of tolbutamide in the presence of clarithromycin (39.43 ± 5.71 to 46.84 ± 5.9 μg/ml); moreover, the mean absorption rate constant showed ~20% increase when clarithromycin was co-administered. It should be noted that the mean bioavailability of tolbutamide increased significantly (~26%) in the presence of clarithromycin. Since the elimination half-life of the drug showed only a slight rise, it appears that the increased bio-availability of tolbutamide may be due to the increased rate of absorption in the presence of clarithromycin. This could be explained by the known effect of macrolide antibiotics on enhancing gastric emptying /12/. This may be one of the reasons for the increased absorption rate of the drug. Another possible reason for increased

TABLE 2

Blood glucose levels (mg/dl) of nine volunteers following administration of tolbutamide (500 mg) (T) and tolbutamide+clarithromycin (250 mg) (C+T)

Time	0 h	1 h	2 h	3 h	4 h	6 h
	T / C+T	T / C+T	T / C+T	T / C+T	T / C+T	T / C+T
# 1	73 / 85	55 / 44*	64 / 48	67 / 42	80 / 78	103 / 75
# 2	99 / 93	47 / 49	48 / 53	69 / 50	67 / 80	90 / 87
# 3	138 / 152	75 / 93	63 / 61	71 / 63	85 / 82	95 / 102
# 4	148 / 142	74 / 62	65 / 60	79 / 63	105 / 102	94 / 98
# 5	168 / 141	78 / 124	70 / 74	99 / 75	117 / 84	63 / 106
# 6	138 / 113	114 / 40*	44 / 62	74 / 67	84 / 116	60 / 60
# 7	88 / 91	66 / 73*	69 / 62	82 / 70	63 / 90	56 / 90
# 8	149 / 140	108 / 72*	68 / 78	64 / 72	65 / 110	78 / 85
# 9	105 / 115	85 / 66*	63 / 48	64 / 67	53 / 62	48 / 70
Mean±SD (T)	123.2±30.56	75.3±22.5	61.6±8.7	74.2±10.52	81.3±20	79.4±21.26
Mean±SD (C+T)	121.2±20.95	77.25±30.49	69±11.79	71±3.42	101±21.56	85.25 ±17.86

* Above 50% reduction in glucose values between T and C+T at 1 h, calculated by:

$$\frac{(T_0 - T_1) - [(C+T)_0 - (C+T)_1]}{T_0 - T_1} \times 100$$

where subscripts 0 and 1 indicate values at 0 h and 1 h.

absorption of the drug may be due to the inhibitory effect of clarithromycin on P-glycoprotein in the gastro-intestinal tract. It has been reported that clarithromycin inhibits renal P-glycoprotein /13/. Although there are no reports in the literature regarding the inhibitory effect of clarithromycin on gastro-intestinal P-glycoprotein, it has been reported that most inhibitors of CYP3A4 also inhibit P-glycoprotein /14/, and clarithromycin is reported to be an inhibitor of CYP3A4. Similarly, it has been observed that the bioavailability of tolbutamide is increased in the presence of diltiazem, a reported P-glycoprotein inhibitor /15/.

The second part of the study was conducted to study the effect of clarithromycin and tolbutamide co-administration on blood glucose levels. Though mean blood glucose levels did not shown any change in the presence of clarithromycin, the individual values (Table 2) demonstrate a marked decrease in blood glucose levels by one hour in five of the nine volunteers. This may be due to the increased absorption rate of tolbutamide in the presence of clarithromycin. Therefore the side effects of giddiness and 'uneasiness' can be correlated with the reduced blood glucose levels and the increased levels of the drug.

Since concomitant administration of clarithromycin and tolbutamide produced some adverse effects, such as 'uneasiness' and giddiness, probably due to a hypoglycemic effect, in subjects during the present study, patients on therapy with tolbutamide should be carefully monitored when clarithromycin is coadministered.

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