PHARMACOKINETIC INTERACTION BETWEEN DILTIAZEM AND TOLBUTAMIDE

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SUMMARY

The effect of co-administered tolbutamide and diltiazem on each drug's pharmacokinetics was studied in eight healthy male volunteers aged 21-25 years, with a 3x3 randomised crossover design. Each subject received orally 60 mg of diltiazem hydrochloride or 500 mg of tolbutamide, or both drugs. The washout period between each treatment was 7 days. Serum levels of diltiazem and tolbutamide were determined by HPLC. Serum profiles were analysed using a non-compartmental model. There was no change in the pharmacokinetics of diltiazem in the presence of tolbutamide. There was ~10% increase in AUC_{0-24} and C_{max} for tolbutamide in the presence of diltiazem.

KEY WORDS

pharmacokinetics, diltiazem, tolbutamide, interaction

INTRODUCTION

Hypertension occurs twice as frequently in patients with diabetes compared to the non-diabetic population /1/. Calcium channel blockers or angiotensin converting enzyme (ACE) inhibitors are the drugs of choice for the treatment of hypertension in a diabetic patient /2/. Among the calcium channel blockers diltiazem is one of the most preferred due to its efficacy and safety. Reports from the literature suggest that diltiazem affects the elimination of some coadministered drugs, probably by its inhibitory effect on cytochrome P-450 enzymes.

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It has been reported that diltiazem causes elevation in blood levels of propranolol, digitoxin, cyclosporin, theophylline, etc. /3-10/.

There are currently no reports available in the literature on any pharmacokinetic interaction of diltiazem and tolbutamide when administered concomitantly. One report suggests that diltiazem may cause insulin resistance in a diabetic patient /11/. The objective of the present study was to investigate the effect on the pharmacokinetics of diltiazem and tolbutamide when the two drugs were co-administered.

MATERIALS AND METHODS

Chemicals

Tolbutamide tablets, 500 mg (Rastinon®, Hoechst Marion Rousell India Ltd.), diltiazem hydrochloride tablets, 60 mg (Dilzem®, Torrent Pharmaceuticals India Ltd.), methanol HPLC (Ranbaxy Chemicals Ltd., India), acetonitrile HPLC (Ranbaxy Chemicals Ltd.). All other chemicals used were of AR grade.

Subjects

Eight healthy human male volunteers aged 21-25 years and weighing 53-65 kg participated in the study after undergoing a thorough physical examination and providing written informed consent. The volunteers had no history of ill-health during the preceding 6 months and none had taken any drug for at least 14 days prior to the study. The protocol was approved by the institutional ethics committee.

Methods

The subjects were randomly divided into three groups and the study was conducted with a crossover design with washout period of 7 days. After an overnight fast (approximately 10-12 hours), volunteers received 40 g glucose in 250 ml of water at 7.30 a.m. followed by either 60 mg diltiazem hydrochloride or 500 mg tolbutamide or the combination at 8.00 a.m. with 200 ml water. No food or drink was permitted for 3 hours after drug administration.

Collection of 3 ml blood samples was made at the following times after drug administration: 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 14 and 24 hours.

Blood was allowed to clot, centrifuged and serum was stored at -20°C until analysis.

Blood glucose levels were determined during the course of study using a glucometer (Ames) and Glucostix® (Bayer Ltd.) at 0, 0.5, 1, 2, 3 and 4 hours after drug administration.

Assay

Tolbutamide was analysed in serum by HPLC using the modified method of Csillag *et al.* /12/. To 0.5 ml of serum in a stoppered test tube, 0.1 ml of chlorpropamide (internal standard) solution (0.01 mg/ml) was added followed by 0.1 ml of 1 N HCl solution. The mixture was vortexed for 1 min, then 5 ml dichloromethane was added and mixed for 15 min in a rotary shaker. The test tubes were centrifuged 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 the mobile phase. About 10-20 µl was injected onto the HPLC column.

The chromatographic conditions were STR (Shinwa Chemical industries Ltd. Japan.) ODS-II column (150 x 4.0 mm) with mobile phase acetonitrile:isopropanol:0.1%v/v orthophosphoric acid (17:17: 66); detector wavelength was 254 nm and flow rate was 1 ml/min.

Diltiazem was estimated in serum by a slight modification of the method reported by Weins *et al.* /13/. The chromatographic conditions were ODS-II Spherisorb column (125 x 4.6 mm) with mobile phase acetonitrile and 0.1% triethylamine solution (1:1). The flow rate was 1.2 ml/min, the detector wavelength was 237 nm and oven temperature was 50°C.

To 0.5 ml of serum, 1 µg of diazepam (internal standard) was added followed by 0.1 ml of 1 M sodium hydroxide and the mixture was vortexed for 30 s. 3 ml of 5% solution of isopropyl alcohol in hexane was added and the mixture vortexed for 2 min. The organic layer was separated in a clean dry test tube and evaporated to dryness under vacuum. The dried residue was reconstituted in 0.1 ml of mobile phase and 0.02 ml was injected onto the column.

Treatment of bioavailability data

The peak serum concentration (C_{max}) and time to peak (t_{max}) were obtained from the experimental data. Elimination half life ($t_{1/2}$), area under the serum concentration curve (AUC), volume of distribution (Vd/f) and clearance (Cls/f) were calculated using a noncompartmental model.

Statistical analysis

The pharmacokinetic parameters for each drug obtained when the two drugs were co-administered were compared with those obtained when each drug was administered on its own by Student's paired t-test. Differences in the sample means were considered significant at $p<0.05$.

RESULTS

None of the volunteers experienced any serious toxic effect related to either diltiazem or tolbutamide. The plots of mean serum concentration of tolbutamide in the presence or absence of diltiazem are shown in Figure 1. The pharmacokinetic parameters of tolbutamide are listed in Table 1. Clearance (CL/f), volume of distribution (Vd/f), elimination rate constant (K_{el}) and elimination half-life ($t_{1/2}$) were not significantly altered in the presence of diltiazem. The mean area under the serum concentration *vs.* time curve (AUC_{0-24}) showed a significant increase of approximately 10% from 410.34 ± 108.92 to 452.81 ± 120.7 μg/ml/h in the presence of diltiazem ($p<0.05$). The mean peak serum concentration (C_{max}) showed ~10% rise from 32.44 ± 5.61 to 35.75 ± 9.62 μg/ml in the presence of diltiazem, but this was not statistically significant.

Figure 2 shows the plots of mean serum concentration of diltiazem in the presence or absence of tolbutamide, and the pharmacokinetic parameters of diltiazem are given in Table 2. There was no significant difference in any of the pharmacokinetic parameters of diltiazem in the presence or absence of tolbutamide.

Blood glucose levels after the administration of tolbutamide with or without co-administration of diltiazem are shown in Figure 3. Diltiazem did not significantly affect the blood glucose decrease caused by tolbutamide.

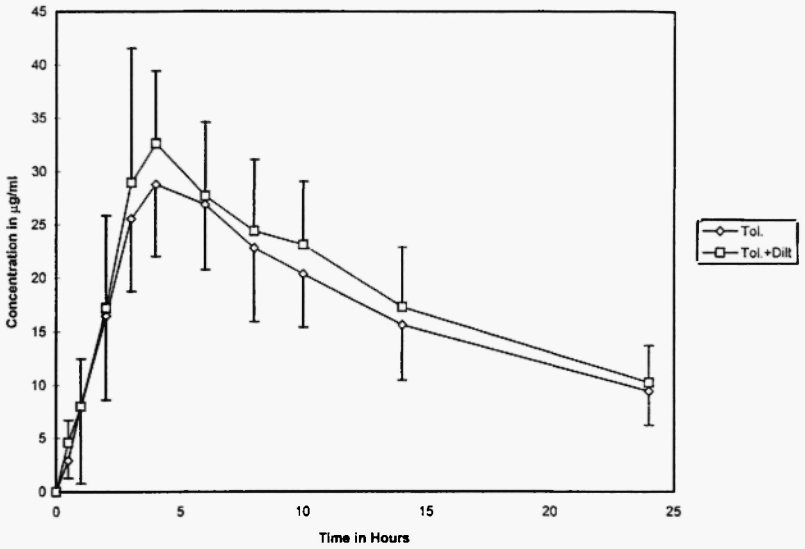

Fig. 1: Mean serum levels of tolbutamide.

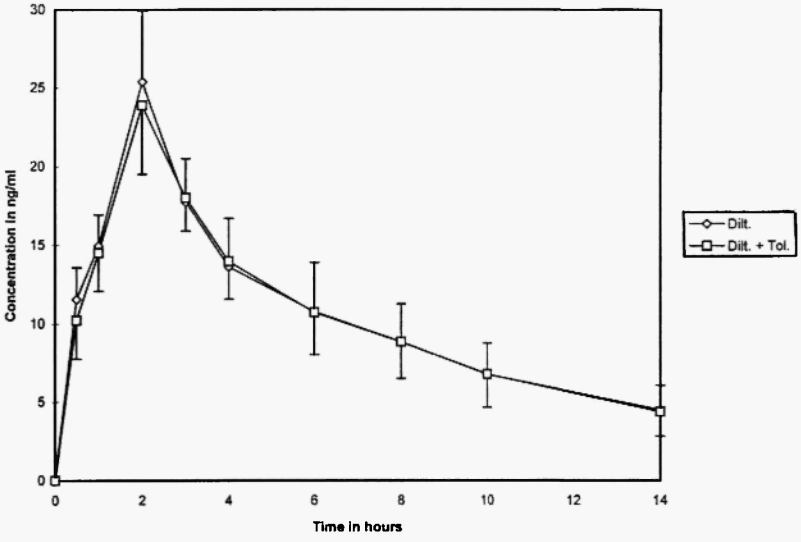

Fig. 2: Mean serum levels of diltiazem.

TABLE 1

Pharmacokinetic parameters of tolbutamide (500 mg) administered on its own and in combination with diltiazem (60 mg)

Pharmacokinetic parameters	**Tolbutamide**	**Tolbutamide and Diltiazem**
AUC_{0-24} (μg/ml/h)	410.34 ± 108.92	452.81 ± 120.7*
$t_{1/2}$ (h)	11.73 ± 2.62	11·90 ± 2.65
K_{el} (h^{-1})	0.0618 ± 0.0176	0.06085 ± 0.01578
Vd/f (l)	21.2 ± 4.81	20.21 ± 7.22
Cl/f (l/h)	1.3 ± 0.359	1·183 ± 0.35
C_{max} (μg/ml)	32.44 ± 5.61	35.75 ± 9.62
t_{max} (h)	4.25 ± 1.16	4.375 ± 1.06

*Significant at $p < 0.05$

TABLE 2

Pharmacokinetic parameters of diltiazem (60 mg) administered on its own and in combination with tolbutamide (500 mg)

Pharmacokinetic parameters	**Diltiazem**	**Diltiazem and Tolbutamide**
AUC_{0-14} (ng/ml/h)	150.38 ± 25.57	145.49 ± 23.08
$t_{1/2}$ (h)	6.55 ± 1.92	6.25 ± 1.77
K_{el} (h^{-1})	0.1148 ± 0.0368	0.1198 ± 038
Vd/f (l)	318.7 ± 71.6	334.14 ± 78.84
Cl/f (l/h)	2923 ± 788.2	2911 ± 690.3
C_{max} (ng/ml)	24.21 ± 4.56	24.07 ± 4.22
t_{max} (h)	2 ± 0	2 ± 0

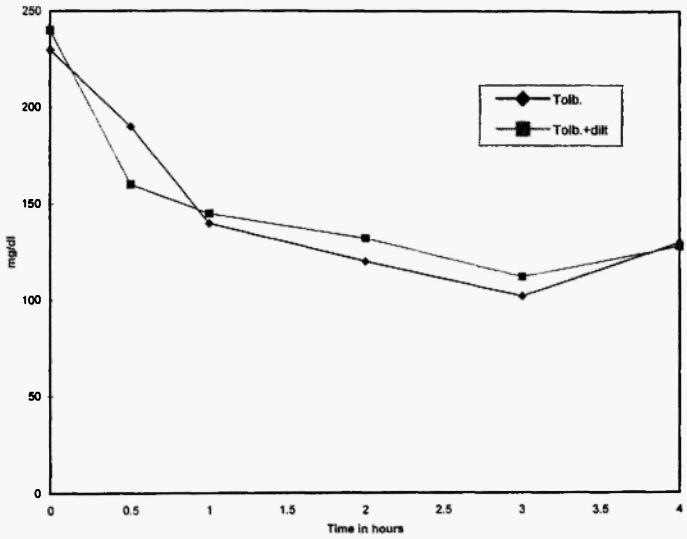

Fig. 3: Mean blood glucose levels.

DISCUSSION

From the present study, it appears that a single 500 mg dose of tolbutamide had no effect on the pharmacokinetics of diltiazem. The pharmacodynamics of tolbutamide seem to be unaffected in the presence of diltiazem. Though the elimination half-life of tolbutamide showed a very slight change (statistically insignificant), the mean area under serum tolbutamide levels *vs.* time (AUC_{0-24}) showed an approximately 10% rise in the presence of diltiazem, which is statistically significant. The mean C_{max} value also showed a the rise of about 10% ($p>0.05$). Two of the eight volunteers showed a 5% decrease in AUC_{0-24} while six volunteers showed a rise in bio-availability ranging from 10-33%. Thus there appears to be some interindividual variation in the effect of diltiazem on the pharmaco-kinetics of tolbutamide. Although genetic variation in the metabolism of tolbutamide is not yet established, the possibility cannot be ruled out /14/. Scott and Poffenbarger reported a wide variability of tolbutamide disappearance rates from plasma after intravenous injection in healthy volunteers, suggesting that genetic factors might control the rate of tolbutamide metabolism /15/. Page and co-workers conducted a screening test in 63 non-diabetic volunteers for slow

metabolizers of tolbutamide. The mean tolbutamide half-life for the 61 screened subjects was 7.5 ± 1.5 h (range 5.2-12.2 h). The remaining two subjects had half-lives of 21.6 and 16.1 h /14/. In the present study, observed values for the elimination half-lives ranged from 7.82-16.14 h (11.73 ± 2.62). One volunteer with elimination half-life of 16.14 h and AUC of 467.65 μg/ml/h showned a decrease in AUC value to 442.13 μg/ml/h with elimination half-life of 15.78 h in the presence of diltiazem. The other subject with elimination half-life 11.82 h showed decreased bioavailability in the presence of diltiazem from 281.13 μg/ml/h to 266.67 μg/ml/h and $t_{1/2}$ changed to 12.92 h. The rest of the volunteers with increased bioavailability in the presence of diltiazem had half-lives ranging from 7.82-13.77. Thus increased or decreased bioavailability in individuals cannot be explained on the basis of genetic variations in the drug metabolising enzymes. A significant increase in mean AUC was observed, even though there was no change in $t_{1/2}$. Since the elimination of tolbutamide seems to be unaffected, the probable reason for this increase may be the inhibition of P-glycoproteins by diltiazem, which is reported to be a substrate and inhibitor of P-glycoproteins /16/. Emi *et al.* have reported that diltiazem increases the absorption of quinidine by the inhibition of P-glycoproteins /17/.

Thus the effect of diltiazem on the metabolism of tolbutamide may not be significant. Since a slight effect was observed only on AUC, while the elimination half-life did not change, and blood glucose levels did not show any significant change, this interaction seems to be of little clinical importance.

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