Indian J Physiol Pharmacol 1992; 36(3) : 205-208

COMPARISON OF BIOVAILABILITY AND PHARMACODYNAMICS OF DILTIAZEM FROM TWO PHARMACEUTICAL PREPARATIONS

SURESH V. DANGE*, DATTATRAYA H. NANDAL, VIDYA S. GOKHALE, KALPANA U. SHAH AND DILEEP B. KADAM

Departments of Pharmacology and Medicine, B. J. Medical College & Sassoon General Hospitals, Pune - 411 001 (Maharastara State)

(Received on February 25, 1992)

Abstract: Diltiazem, a calcium channel blocker, is used in multiple divided doses daily, due to its short elimination half-life. Hence, administration as a modified release (MR) formulation is suggested. In this double blind cross-over trial, the pharmacokinetics and pharmacodynamics of diltiazem was studied in eight healthy Indian adults. Diltiazem was administered as single dose (60 mg) of the two formulations viz. immediate release (IR) and MR. Venous blood samples, for estimation of diltiazem by HPLC, were collected at frequent intervals and BP, HR and ECG were monitored during the 12h study period. With MR formulation, plasma half-life was significantly ($P< 0.05$) prolonged (6.25 ± 1.2 h vs. 2.69 ± 0.2 h), the extent of alterations in BP, HR and PR interval was significantly less, while the duration of prolongation of PR interval was significantly more as compared to IR formulation. Therefore, MR formulation of diltiazem has better pharmacokinetic and pharmacodynamic profile as compared to IR formulation.

Key words: diltiazem kinetics dynamics modified release formulation

INTRODUCTION

Calcium entry blockers (CaA) are one of the most frequently prescribed classes of drugs. These agents are particularly beneficial for selected patient groups like the elderly and the black patients with hypertension (1) and angina. Diltiazem, a member of this class, has important and clinically significant differences in its pharmacodynamic and hemodynamic actions when compared to nifedipine. Diltiazem has an elimination half-life of 3.2 ± 1.3 hours (2), which necessitates three or four daily doses. Such administration may lead to fluctuations in plasma concentrations, which could coincide with periods of increased catecholamines, higher blood pressure levels and increased MVO and peak levels, which could cause episodes of bradycardia. Taking these factors into account, a modified release (MR) formulation of diltiazem hydrochloride was developed for providing consistent plasma concentrations avoiding the peaks and troughs.

The objective of this study was to investigate the bioavailability, pharmacokinetics and pharmacodynamics of the MR formulation and compare them with the unmodified (IR) formulation.

METHODS

Eight healthy male volunteers were selected for the study and informed written consent obtained from them. The protocol for the study was aproved by the Institutional Ethics Committee and by the Drug Controller of India. The mean age of the participants was 19.38 years (range 19 to 21 years) and their mean weight 56.19 kg (53 to 61 kg). Clinical, biochemical and hematological studies were carried out on each subject before the study. There were no abnormal findings. Each subject had a normal 12-lead ECG.

This study was carried out using a double blind, cross-over design. The test preparation was diltiazem 60 mg (MR) tablets modified to provide slow release and sustained plasma concentrations over 6 to 8 hours. These tablet were compared to the regular diltiazem 60 mg (IR) tablets from which the drug release is immediate.

*Corresponding Author

The subjects did not take any medication during 8 days preceding the first study day. Further, for 24 hours preceding the study day, they did not take alcoholic and caffeine-containing beverages. On the study day, the subjects reported to the Clinical Pharmacology Unit at 7.30 a.m. After a rest period of half an hour, a 12-lead ECG was recorded and the blood pressure was taken using a standard mercury sphygmomanometer with the subjects in the supine position using the right arm. Korotkoff sounds I and V were used to record the systolic and diastolic pressures respectively. After taking blood sample 0, the test drugs were given in a randomised manner so that half the number of subjects received the IR formulations and the other half the MR formulations. Blood pressure and heart rate were taken after 1, 2, 4, 6, 8, 10 and 12 hours after the administration of the tablets. ECG was recorded 2, 4, 6, 8 and 12 hours after the drug intake. The PR interval expressed in milliseconds, was determined from the mean of five consecutive heart beats from leads II or V. Blood samples were taken $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, 4, 8, 10 and 12 hours after the drug intake. Blood samples were centrifuged at 1000g immediately after collection and the plasma was transferred to screw-top plastic vials. Heparin-2 units/ml in normal saline was used to flush the i.v. cannula to prevent clotting. The samples were stored in a deep freeze at -20°C till they were analysed. A light meal was given at lunch time at least 4 hours after drug administration.

After a 10 days interval during which the subjects did not take any medication, the entire procedure was repeated with the drug intake crossed over. The subjects were asked to report any unusual feeling or effects. Any such reports were recorded.

Plasma diltiazem was measured by high performance liquid chromatography [Waters Assoc. (Milford, MA, USA) Model 510 and Perken Elmer LC290 variable wavelength UV spectrophotometer], using diphenhydramine as the internal standard and sensitive to 2 ng/ml (3).

The plasma concentration values were plotted againt time to obtain - Plasma concentation - time curves for the two preparations, from which the parmacokinetic parameters Cmax, tmax and t1/2 were calculated. The area under the curve (AUC) was calculated by the trapezoidal method.

The data were analysed statistically using the Student's paired "t" test with a "p" less than 0.05 as the level of significance.

RESULTS

Pharmacokinetics : Table I and Fig. 1 show the pharmacokinetic profile of diltiazem after oral administration of the IR and MR formulations. Absorption of diltiazem from IR formulation was quicker as compared to that with MR formulation. Although the Cmax was higher with IR formulation, the plasma levels declined rapidly. In contrast to this, the Cmax was lower with MR formulation, but the plasma levels were more consistent. There was no significant difference in the total amount of diltiazem absorbed from these two preparations.

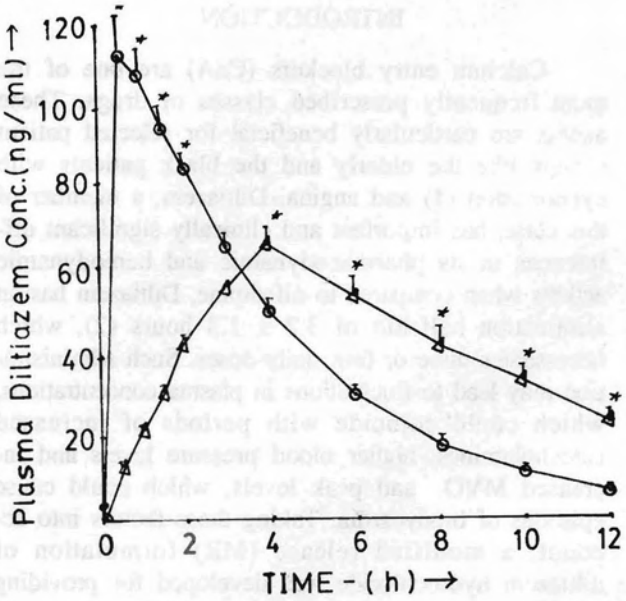

Fig. 1 : Plasma concentration versus time curves of two formulations of diltiazem.
n = 8, *P < 0.05, Concentrations are mean ± SE
IR : Immediate Release Formulation
MR : Modified Release Formulation

TABLE I: Pharmacokinetics of the two diltiazem formulations.

	IR	*MR*
Cmax (ng/ml)	120.50 ± 21.90	67.50 ± 9,54*
tmax (h)	0.58 ± 0.30	3.75 ± 0,43*
tl/2 (h)	2.69 ± 0.24	6.25 ± 1.20*
AUC (ng.h/ml) 0-12 h	483.65 ± 91.70	500.25 ± 87.56

n = 8 each, Mean ± SD, *P < 0.05

Blood pressure : Table II shows the effect of the two formulations of diltiazem on systolic and diastolic blood pressures. There was a significant fall in the SBP at 2 to 4 hours after the IR formulation and at 4 hours after the MR formulation. The DBP fell significantly (P< 0.05) at 1, 2, 4, and 6 hours with the IR formulation and only at 2 and 4 hours with the MR formulation. The degree of fall in DBP was significantly (P< 0.05) less with MR formulation than the IR formulation.

TABLE II : Effect of the two formulations of diltiazem on the blood pressure.

Time (h)	*Blood presure (mm Hg)*			
	IR		*MR*	
	SBP	*DBP*	*SBP*	*DBP*
0	11.5.75 ± 2.05	76.00 ± 1.58	114.50 ± 2.84	75.25 ± 2.47
1	113.50 ± 2 60	70.00 ± 1.80#	114.00 ± 2.80	74.50 ± 2.00
2	110.50 ± 3.09#	66.00 ± 1.73#	113.00 ± 2.88	72.50 ± 2.0*#
4	111.50 ± 2.52#	68.50 ± 1.83#	111.50 ± 2.84#	71.25 ± 2.9*#
6	114.75 ± 1.85	70.50 ± 1.96#	113.75 ± 2.97	70.75 ± 3.14
8	115.25 ± 2.34	69.00 ± 2.21	112.75 ± 3.02	69.00 ± 3.50
10	116.25 ± 2.41	71.50 ± 1.45	114.25 ± 1.92	73.75 ± 2.75
12	117.50 ± 2.42	72.25 ± 0.82	116.00 ± 2.55	75.00 ± 1.97*

N = 8 each, *# : P < 0.05, Values are mean ± SE, SBP - Systolic Blood Pressure, DBP - Diastolic Blood Pressure, # - Comparison with initial value in the same group, * - Comparison of IR Vs. MR

Heart rate : Table III shows the effect of the two formulations on the heart rate. There was a significant (P < 0.05) reduction in the heart rate at 2 and 4 hours after IR formulation but only at 4 hours after the MR formulation. The degree of reduction was significantly (P< 0.05) less with the MR formulation.

TABLE III : Effect of the formulations of diltiazem on heart rate (beats/min) and PR interval (msec).

Time (h)	*IR*		*MR*	
	Heart rate (beats/min	*PR Interval (m sec)*	*Heart rate (beats/min)*	*PR interval (msec)*
0	71.38 ± 3.68	130.00 ± 6.12	72.00 ± 2.50	130.00 ± 6.12
2	65.50 ± 3.25#	168.75 ± 14.52#	71.63 ± 3.20*	156.25 ± 7.89*#
4	67.63 ± 2.45#	142.50 ± 11.24#	67.87 ± 3.54#	162.50 ± 13.40*#
6	69.32 ± 2.86	138.00 ± 8.75	68.00 ± 3.85	150.00 ± 10.25*#
8	71.45 ± 3.50	134.10 ± 7.25	68.84 ± 3.90	144.50 ± 5.93*#
12	73.26 ± 3.88	132.50 ± 6.06	72.20 ± 3.54	131.75 ± 6.02

n = 8 each #* : P < 0.05, Values are mean ± SE, # - Comparison with initial value in the same group, * - Comparison between IR & MR

PR Interval : The effect of the IR form of diltiazem is shown in Table III. There was a significant ($P < 0.05$) prologation of the PR interval only at 2 and 4 hours after the IR formulation but at 2, 4, 6 and 8 hours with the MR formulation. But the increase of PR interval was significantly ($P < 0.05$) less with the MR than with the IR formulation.

Adverse effects : Five subjects complained of headache, of mild to moderate intensity with the IR formulation, while none reported any side effect on MR formulation. Three of subjects with headache were given paracetamol 500 mg.

DISCUSSION

In the present study, the pharmacokinetics and pharmacodynamics of a single dose of diltiazem 60 mg administered as an IR formulation were compared with those of a MR formulation. The pharmacokinetics of the two preparations differed significantly, except for the AUCs. This latter finding shows that the amount of diltiazem absorbed from the MR formulation is about the same from the IR formulation. This is consistent with the observations by other investigators that physical differences in formulation alter rate of absorption but not the absolute bioavailability (4). The difference in pharmacokinetic profile might be due to differences in the rate of dissolution of the two preparations viz. about 45% of the drug at 1/2 h with MR formulation in contrast to 100% released within 10 minutes with IR formulation (data on file).

With the MR formulation plasma concentration of diltiazem was above 40 ng/ml for 8 hours, in contrast to only less than 5 hours with the IR formulation. Optimum therapeutic concentration has been reported to be 40 ng/m (5).

Under steady state conditions during multiple dose therapy, the MR formulation can be expected to provide consistent plasma levels of diltiazem while with the IR formulation the levels would be fluctuating between the peaks and troughs.

Administration of 20 mg of diltiazem i.v. has been reported to cause $14.3 \pm 5.4\%$ increase in the PR interval in patients of paroxysmal atrial tachycardia (6). In the present study, we observed a maximum increase in the PR interval, of 30% at 2 hours after the IR formulation and of 25% at a 4 hours after the MR formulations (Table III). However, since the first ECG was taken 2 hours after the IR formulation, the possibility of an earlier peak cannot be ruled out.

Large inter-individual variations were observed in all the pharmacodynamic effects of diltiazem in this study. Similar variations have been reported (7).

Headache was reported only with IR formulation. Its occurrence within 30 to 90 minutes of the drug intake suggests a possible relation with the earlier and faster build up of plasma concentrations.

In this acute study, administration of the MR formulation caused significantly ($P < 0.05$) less alterations in the pharmacodynamic parameters studied viz. systolic and diastolic blood pressures, PR interval and heart rate. MR formulations are designed to minimize wide fluctuations in the plasma levels of active drugs and to reduce type A toxicity, and to prolong the duration of therapeutic effect. The MR formulation of diltiazem used in this study was found to fulfil these objectives. However, studies in larger number of patients, especially the middle aged and the elderly, as well as in steady states using multiple doses would be necessary to confirm these findings since age and duration of therapy have been reported to modify diltiazem kinetics (7).

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the co-operation by Dr. (Mrs.) Phadke, M.A., Prof. & Head of Pediatics, technical assistance by Smt. Khedkar and the financial assistance from Research Society, B.J. Medical College. and Sassoon General Hospitals, Pune and Anglo-French Drug Co., Bangalore.

REFERENCES

1. Butler FR. Age and cardiovascular response adaptation: determinants of an antihypertensive treatment concept primarily based on beta-blockers and calcium entry blockers. *Hypertension* 1983; 5 (5 pt 2) III : 94-100.
2. Chaffman M, Brogden RN. Diltiazem : A review of its pharmacological properties and therapeutic efficacy. *Drugs* 1985; 29 : 387-454.
3. Montamat SC, Abernathy DR, Mitchell JR. High performance liquid chromatographic determination of diltiazem and its major metabolites, N-monodemethyl-diltiazem and desacetyldiltiazem, in plasma. *J Chromatogr* 1987; 415 : 203-207.
4. Bighley LD, Dimmitt DC, McGraw BF. Bioavailability of Diltiazem hydrochloride formulations. *Clinical Research* 1980; 28 : 587A.
5. Hosada S Clinical experience of diltiazem. In Bing RH Ed. New Drug Therapy with Calcium Antagonist. Diltiazem Hakone Symposium, 1978. *Amsterdam, Excerpta Medica* 1978; 230-241.
6. Smith MS, Verghese CP, Shand DG et al. Pharmacokinetic and pharmacodynamic effects of diltiazem. *Am J. Cardiol* 1983; 51 : 1369-1374.
7. Montamat SC, Abernathy DR. Calcium antagonists in geriatric patients : Diltiazem in elderly persons with hypertension. *Clin Pharmacol Ther* 1989; 45 : 682-691.