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THE RELATIVE BIOAVAILABILITY OF TWO MARKETED CONTROLLED RELEASE DILTIAZEM DOSAGE FORMS AT STEADY STATE IN HEALTHY VOLUNTEERS

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ABSTRACT

This study was conducted to determine the relative bioavailability of Dilacor™ XR capsules compared to Cardizem® CD capsules at both low ($180\,mg\,d^{-1}$) and high ($540\,mg\,d^{-1}$) dose levels. Trough and serial plasma samples were obtained and pharmacokinetic parameters were calculated from the steady state concentration–time profiles. Mean steady state plasma diltiazem concentrations ($AUC_{ss}(0–24)$) of Dilacor XR were 19% and 26% lower than those of Cardizem CD for the $180\,mg\,d^{-1}$ and $540\,mg\,d^{-1}$ dose levels, respectively. In addition, Dilacor XR had lower mean $C_{max,ss}$, $T_{max,ss}$, $C_{min,ss}$, and trough values than Cardizem CD with percentage differences ranging from 17% to 29%. The variability (%CV) in the data from the Dilacor XR treatments was higher for each calculated pharmacokinetic parameter compared to the Cardizem CD treatments. The %CV for Dilacor XR ranged from 34% to 104% while the %CV for Cardizem CD ranged from 21% to 49%. From these results, it may be concluded that Dilacor XR is not bioequivalent to Cardizem CD at steady state doses of $180\,mg\,d^{-1}$ and $540\,mg\,d^{-1}$.

KEY WORDS: diltiazem; pharmacokinetics; bioequivalence; bioavailability

INTRODUCTION

Calcium channel blockers, which act by interfering with calcium-mediated events in excitation–contraction coupling in smooth muscle, particularly coronary arteries, are commonly used in the treatment of mild or moderate hypertension and angina. Three such agents are diltiazem, nifedipine, and verapamil, all of which have rather short elimination half-lives and therefore require divided daily dosing.[1] The administration of these agents in a single daily dose is of considerable interest. This study describes the pharmacokinetic characteristics of two once-daily diltiazem hydrochloride formulations currently available in the United States, Cardizem® CD (Marion Merrell Dow Inc.) and Dilacor™ XR (Rhône Poulenc Rorer Pharmaceuticals Inc.). Specifically, the steady state relative bioavailability of diltiazem at two different dose levels is examined.

To accurately characterize the bioavailability of diltiazem, dosing to steady state plasma concentrations (3–5 d) is required because of its nonlinear

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pharmacokinetics. The area under the plasma diltiazem concentration–time curve (AUC) increases after multiple dosing, indicating that the first-pass clearance decreases upon chronic administration.[2] Because of extensive first-pass hepatic metabolism, only approximately 30–40% of diltiazem is available after a single oral dose.[3] It is metabolized into several compounds including desacetyldiltiazem and N-desmethyldiltiazem which have some pharmacologic activity (50% and 20% of the potency of parent drug, respectively).[4,5] These metabolites are detectable in plasma within 30 min of taking diltiazem. The elimination half-life of orally administered diltiazem averages about 4·5 h (range, 2–11 h).[3,6]

METHODS

This study was an open label, four-way, randomized, complete crossover design using healthy, male subjects between the ages of 19 and 45. The subjects were chosen after completing a thorough medical history, physical examination, routine blood and urine laboratory tests, and obtaining informed consent. None of the subjects had a history of cardiovascular, renal, hepatic, gastrointestinal, or hematologic disease. The physical examination, blood, and urine laboratory tests were repeated after completion of the study. No other drugs were allowed throughout the study. Subjects were randomly assigned to one of four treatments with a 7 d washout period between treatments. The four treatments were (i) one 180 mg Cardizem CD capsule given once daily for 7 d; (ii) one 180 mg Dilacor XR capsule given once daily for 7 d; (iii) two 180 mg (360 mg total dose) Cardizem CD capsules given for 1 d, then three 180 mg capsules (540 mg total dose) given once daily for 6 d; and (iv) two 180 mg (360 mg total dose) Dilacor XR capsules given for one day, then three 180 mg capsules (540 mg total dose) given once daily for 6 d. Diltiazem HCl was administered as Cardizem CD 180 mg capsules (lot No. K11177) and Dilacor XR 180 mg capsules (lot No. J83505). All drug administrations were at 7 a.m. with 240 mL of room-temperature water.

Baseline blood (plasma) samples were obtained prior to dosing on day 1. Trough plasma samples were obtained on days 2–7 just before dosing. Serial plasma samples were collected on day 7 at 1, 2, 4, 6, 8, 10, 12, 14, 16, and day 8 at 18, 20, 22, and 24 h following the final diltiazem HCl dose. Plasma samples were stored at −20 °C until assayed.

Twelve-lead electrocardiograms (ECGs), heart rate, and blood pressure measurements were obtained before and after the study and 12 h following dosing on days 1, 2, and 4. Heart rate and blood pressure measurements were also taken before each morning dose.

A high-performance liquid chromatographic (HPLC) method using ultraviolet detection was employed to determine the plasma concentrations of diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem. The lower limit of

Table 1. Within-treatment comparisons of days 6, 7, and 8 mean diltiazem trough values for Dilacor XR and Cardizem CD steady state doses of 180 mg d^{-1} (treatments A and B) and 540 mg d^{-1} (treatments C and D)

Treatment	Day	Adjusted mean	Days compared	% difference between days	*p* value
A	6	36·35	7–6	1·8	0·8297
(Cardizem CD)	7	37·01	8–6	3·0	0·7231
	8	37·44	8–7	1·2	0·8891
B	6	29·07	7–6	−0·7	0·9532
(Dilacor XR)	7	28·87	8–6	3·1	0·7899
	8	29·96	8–7	3·8	0·7452
C	6	50·21	7–6	0·3	0·9638
(Cardizem CD)	7	50·34	8–6	−1·5	0·7997
	8	49·46	8–7	−1·8	0·7648
D	6	40·09	7–6	−7·3	0·3920
(Dilacor XR)	7	37·15	8–6	−0·2	0·9805
	8	40·01	8–7	7·7	0·4055

quantitation was 6·25 ng mL^{-1} for diltiazem and 3·12 ng mL^{-1} for desacetyldiltiazem and N-desmethyldiltiazem.

The following steady state pharmacokinetic parameters for diltiazem, N-desmethyldiltiazem, and desacetyldiltiazem were derived from the individual plasma concentration–time profiles; area under the plasma concentration–time curve during the 24 h period following the final 7 a.m. dose ($AUC_{ss}(0–24)$) calculated by the trapezoidal rule; maximum plasma concentration observed during the 24 h following the final 7 a.m. dose ($C_{max,ss}$); minimum plasma concentration observed during the 24 h following the final 7 a.m. dose ($C_{min,ss}$); and time to reach $C_{max,ss}$ ($t_{max,ss}$). The ratio of $C_{max,ss}$ to $C_{min,ss}$ (RATIO) on day 7 was calculated and the relative bioavailability of Dilacor XR as compared to Cardizem CD was determined by calculating the mean of individual relative bioavailabilities based on diltiazem $AUC_{ss}(0–24)$. Also, trough plasma concentration (diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem) values from samples taken just before dosing on days 6, 7, and 8 were summarized.

Pharmacokinetic parameters were analyzed by means of analysis of variance (ANOVA), with a model appropriate for a four-period, four-treatment crossover design. The primary analysis was chosen using the following criteria. If the original data met the model assumptions of (i) equality of variance among treatment groups residuals (tested using Levine's test) and (ii) normality of distribution for treatment groups residuals (tested using the Shapiro–Wilk test) then the untransformed data were used for analysis. If not, but log-transformed data did meet all model assumptions, then the log-transformed data were used for analysis. If neither the original nor the

Table 2. Mean steady state diltiazem pharmacokinetic parameters for 180 mg d^{-1} treatments A (Cardizem CD) and B (Dilacor XR), $n = 23$, and 540 mg d^{-1} treatments C (Cardizem CD) and D (Dilacor XR), $n = 22$

Variable	TRT	Mean (%CV)	% pairwise difference[a,b]	90% CI[b]	p value[b,c]
$AUC_{ss}(0–24)$	A	1408·73 (27·66)			
(ng h mL^{-1})	B	1139·93 (47·00)	−18·8	−31·4, −6·2	0·0156
	C	6068·69 (23·24)			
	D	4479·76 (38·77)	−26·3	−35·3, −17·2	0·0001
$C_{max,ss}$	A	91·83 (29·62)			
(ng mL^{-1})[d]	B	74·49 (33·80)	−17·1	−26·4, −8·8	0·0003
	C	390·54 (20·99)			
	D	302·69 (34·65)	−23·5	−30·7, −15·8	0·0001
$t_{max,ss}$ (h)[d]	A	7·74 (40·72)			
	B	6·61 (66·70)	−28·6	−42·9, 14·3	0·0082
	C	7·55 (49·03)			
	D	5·09 (55·20)	−28·6	−57·1, 0·0	0·0023
$C_{min,ss}$	A	30·02 (35·49)			
(ng mL^{-1})	B	24·06 (67·75)	−19·5	−38·9, −0·0	0·0994
	C	119·82 (41·93)			
	D	95·18 (65·08)	−20·7	−35·7, −5·6	0·0251
Trough	A	36·93 (31·92)			
(ng mL^{-1})	B	29·30 (54·82)	−20·5	−34·8, −6·1	0·0208
	C	150·00 (35·00)			
	D	117·25 (50·27)	−21·9	−32·8, −11·1	0·0013
Ratio[d]	A	3·39 (48·54)			
($C_{max,ss}/C_{min,ss}$)	B	3·91 (50·79)	6·6	−12·8, 36·8	0·3209
	C	3·69 (40·66)			
	D	5·52 (103·45)	13·6	−8·4, 71·3	0·9827
F[e] (relative	A	1·00	NA[f]	NA	NA
bioavailability)	B	0·809	NA	NA	NA
	C	1·00	NA	NA	NA
	D	0·738	NA	NA	NA

[a]% pairwise difference, treatment B compared to treatment A and treatment D compared to treatment C.
[b]Based on adjusted means from ANOVA or on nonparametric estimates.
[c]p value, pairwise p value from ANOVA.
[d]Statistical analysis done using rank-transformed data.
[e]F, from $AUC_{ss}(0–24)$.
[f]NA, not applicable.

log-transformed data met all model assumptions, then the rank-transformed data were used for analysis.

RESULTS

Twenty-two of 28 subjects successfully completed the study and were included in the pharmacokinetic analysis. The average age of the 22 subjects was 29·8

Table 3. Mean steady state desacetyldiltiazem pharmacokinetic parameters for 180 mg d^{-1} treatments A (Cardizem CD) and B (Dilacor XR), $n = 23$, and 540 mg d^{-1} treatments C (Cardizem CD) and D (Dilacor XR), $n = 22$

Variable	TRT	Mean (%CV)	% pairwise difference[a,b]	p value[b,c]
$AUC_{ss}(0–24)$	A	285·70 (113·24)		
(ng h mL^{-1})[d]	B	264·03 (123·91)	−15·3	0·0734
	C	1276·09 (93·95)		
	D	1025·08 (113·86)	−22·9	0·0001
$C_{max,ss}$	A	14·47 (108·75)		
(ng mL^{-1})[d]	B	13·40 (112·09)	−14·7	0·0400
	C	62·51 (88·48)		
	D	51·55 (101·42)	−18·9	0·0004
$t_{max,ss}$ (h)	A	14·96 (42·83)		
	B	12·73 (62·58)	−15·3	0·1766
	C	14·00 (29·24)		
	D	10·36 (71·63)	−25·8	0·0381
$C_{min,ss}$	A	9·57 (111·68)		
(ng mL^{-1})[d]	B	8·77 (140·29)	−15·3	0·1727
	C	42·83 (102·75)		
	D	33·74 (127·58)	−20·7	0·0004
Trough	A	11·21 (118·03)		
(ng mL^{-1})[d]	B	9·38 (133·60)	−23·2	0·0188
	C	50·11 (97·51)		
	D	39·82 (119·19)	−24·1	0·0003
Ratio[e]	A	1·57 (19·45)		
($C_{max,ss}/C_{min,ss}$)	B	1·73 (33·11)	9·5	0·2777
	C	1·67 (36·16)		
	D	2·11 (48·70)	21·0	0·0267

[a]% pairwise difference, treatment B compared to treatment A and treatment D compared to treatment C.
[b]Based on adjusted means from ANOVA or on nonparametric estimates.
[c]p value, pairwise p value from ANOVA.
[d]Statistical analysis done using rank-transformed data.
[e]Statistical analysis done using log-transformed data.

years (SD, 8·11), with an average height of 179·6 cm (SD, 5·55) and weight of 75·1 kg (SD, 10·21).

Steady state plasma diltiazem concentrations were achieved by day 6 for each treatment (see Table 1). A comparison, within each of the four treatments, between plasma diltiazem trough concentrations measured on days 6, 7, and 8 produced p values ranging from 0·40 to 0·98 demonstrating no appreciable change by day 6.

Mean pharmacokinetic parameters ($AUC_{ss}(0–24)$, $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, trough, and RATIO), derived from the plasma diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem concentration–time curves, along with a summary

Table 4. Mean steady state N-desmethyldiltiazem pharmacokinetic parameters for 180 mg d^{-1} treatments A (Cardizem CD) and B (Dilacor XR), $n = 23$, and 540 mg d^{-1} treatments C (Cardizem CD) and D (Dilacor XR), $n = 22$

Variable	TRT	Mean (%CV)	% pairwise difference[a,b]	p value[b,c]
$AUC_{ss}(0–24)$ (ng h mL^{-1})[d]	A	583·15 (22·71)		
	B	500·24 (30·65)	−12·0	0·0025
	C	2058·85 (18·73)		
	D	1605·51 (31·90)	−19·3	0·0001
$C_{max,ss}$ (ng mL^{-1})[d]	A	30·84 (23·83)		
	B	27·50 (22·26)	−8·3	0·1485
	C	109·93 (19·54)		
	D	87·04 (28·74)	−19·1	0·0001
$t_{max,ss}$ (h)	A	10·09 (34·07)		
	B	7·91 (60·72)	−21·5	0·0638
	C	10·73 (34·30)		
	D	7·27 (56·00)	−32·0	0·0049
$C_{min,ss}$ (ng mL^{-1})	A	16·69 (26·10)		
	B	12·80 (41·54)	−23·4	0·0015
	C	55·40 (27·51)		
	D	43·47 (49·18)	−21·4	0·0018
Trough (ng mL^{-1})	A	19·17 (23·63)		
	B	15·75 (36·09)	−18·0	0·0029
	C	64·55 (22·23)		
	D	50·60 (38·32)	−21·4	0·0001
Ratio[d] ($C_{max,ss}/C_{min,ss}$)	A	1·92 (24·86)		
	B	2·47 (44·83)	19·9	0·0283
	C	2·09 (26·07)		
	D	2·38 (46·48)	5·8	0·9197

[a]% pairwise difference, treatment B compared to treatment A and treatment D compared to treatment C.
[b]Based on adjusted means from ANOVA or on nonparametric estimates.
[c]p value, pairwise p value from ANOVA.
[d]Statistical analysis done using rank-transformed data.

of the statistical comparisons are found in Tables 2–4. Plots of the mean plasma diltiazem concentration–time profiles are presented in Figures 1 and 2.

As seen in Table 2, mean steady state plasma diltiazem concentrations of Dilacor XR were 19% and 26% lower than those of Cardizem CD for the 180 mg d^{-1} and 540 mg d^{-1} dose levels, respectively, based on $AUC_{ss}(0–24)$. In addition, Dilacor XR had lower mean diltiazem $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, and trough values than Cardizem CD with percentage differences ranging from 17% to 29% at both dose levels. The p values show that mean diltiazem $AUC_{ss}(0–24)$, $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$ (540 mg d^{-1} dose only), and trough values were significantly ($p < 0·05$) lower in the Dilacor XR treatments compared to the Cardizem CD treatments at both dose levels except where indicated.

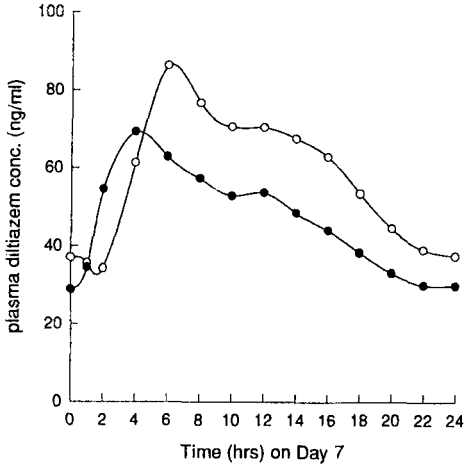

Figure 1. Steady state mean plasma diltiazem concentrations after 180 mg d^{-1} dosing in 23 healthy subjects: ●, Dilacor XR; ○, Cardizem CD

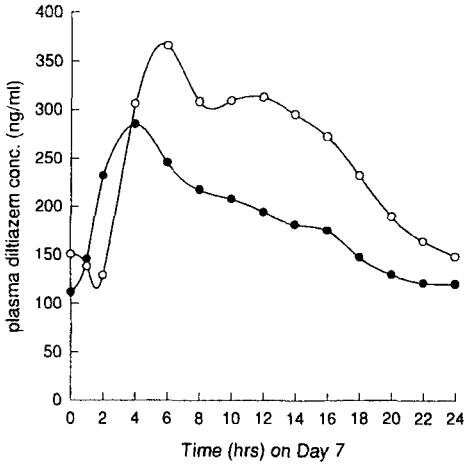

Figure 2. Steady state mean plasma diltiazem concentrations after 540 mg d^{-1} dosing in 22 healthy subjects: ●, Dilacor XR; ○, Cardizem CD

For the metabolites, desacetyldiltiazem and N-desmethyldiltiazem, the trends are similar (see Tables 3 and 4). The Dilacor XR treatments had lower (8–32%) mean $AUC_{ss}(0–24)$, $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, and trough values compared to the Cardizem CD treatments. The differences were more pronounced at the 540 mg d^{-1} dose level than the 180 mg d^{-1} dose level for each parameter.

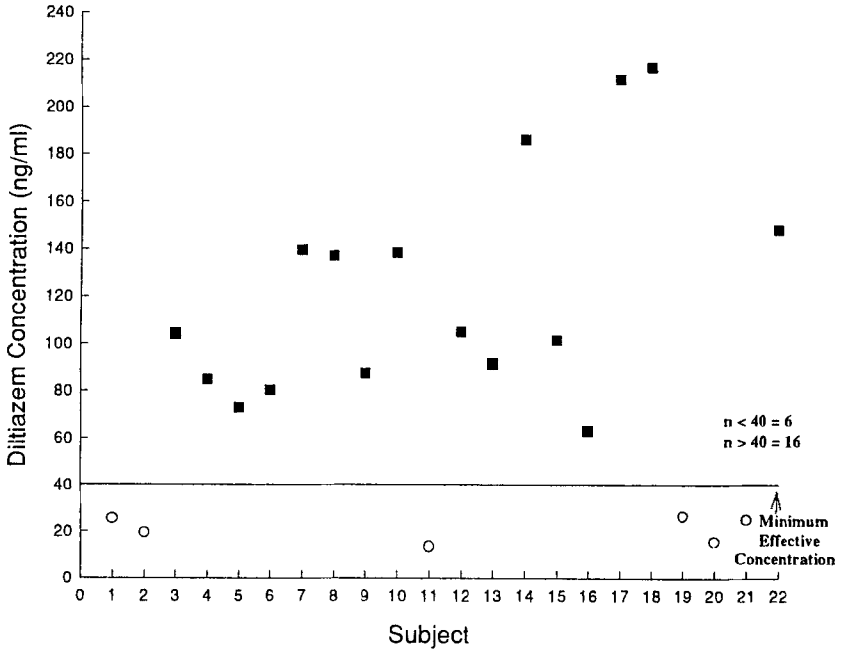

Figure 3. Minimum plasma diltiazem concentrations from Dilacor XR 540 mg d^{-1} steady state dosing

The coefficient of variation percentage (%CV, a measure of variability within treatment groups) for the Dilacor XR treatments was greater than for the Cardizem CD treatments as seen in Tables 2–4. For example, the 180 mg d^{-1} Dilacor XR treatment coefficient of variation was 33·80% compared to 29·62% for the Cardizem CD for mean diltiazem $C_{max,ss}$. The 540 mg d^{-1} treatment level variation of $C_{max,ss}$ was 34·65% for Dilacor XR compared to 20·99% for Cardizem CD.

DISCUSSION

This study demonstrates that Dilacor XR is not bioequivalent to Cardizem CD under steady state conditions across the dose range of 180–540 mg d^{-1}. Key Dilacor XR steady state diltiazem pharmacokinetic parameters were significantly lower than those of Cardizem CD at each dose level. At the 540 mg d^{-1} dose level, each calculated mean diltiazem pharmacokinetic parameter, with the exception of RATIO, showed a greater than 20% mean difference between dosage forms. The lower $AUC_{ss}(0–24)$ and $C_{max,ss}$ values indicate that less absorption of diltiazem HCl from the Dilacor XR

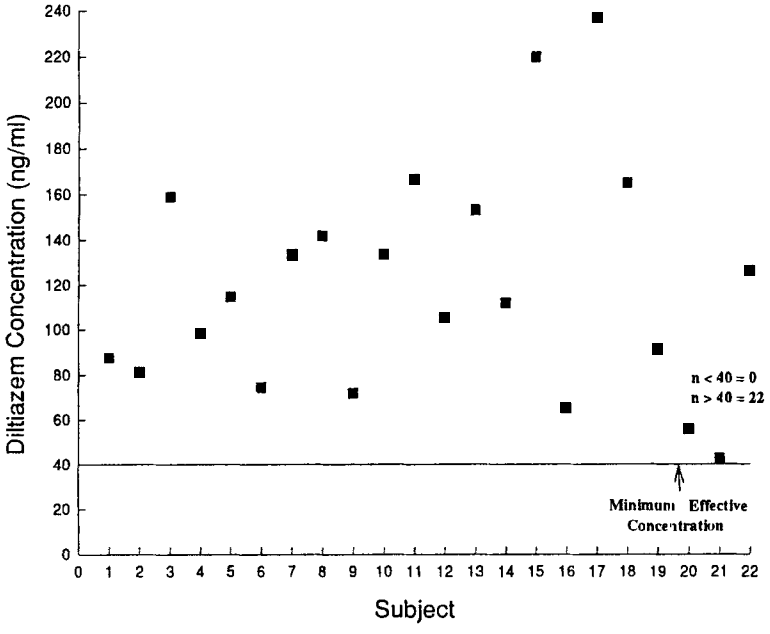

Figure 4. Minimum plasma diltiazem concentrations from Cardizem CD 540 mg d^{-1} steady state dosing

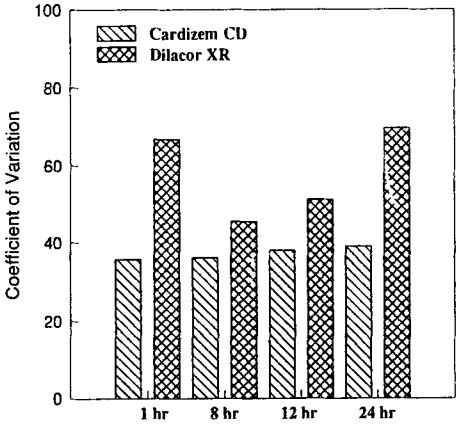

Figure 5. Variability (%CV) at selected hours of plasma diltiazem levels between Cardizem CD and Dilacor XR at 180 mg d^{-1} steady state dosing

formulation compared to the Cardizem CD formulation takes place. This indicates the need for higher doses of Dilacor XR to achieve the same plasma diltiazem concentrations as with Cardizem CD.

It has been well documented that there is a circadian rhythm associated with cardiac events such as angina, myocardial ischemia, hypertension, cerebrovascular strokes, and sudden cardiac death.[7–9] In order to attempt to reduce the morbidity and mortality associated with these events, it is necessary to maintain therapeutic drug plasma concentrations throughout the dosing interval. Some of the literature suggests that diltiazem has a minimum therapeutic plasma concentration of $40\,ng\,mL^{-1}$.[10–12] Figure 3 shows that at the higher, $540\,mg\,d^{-1}$, treatment level on day 7, six subjects taking Dilacor XR had minimum plasma diltiazem concentrations which dropped below the $40\,ng\,mL^{-1}$ minimum effective concentration while Figure 4 shows that none of the same subjects taking the same dose of Cardizem CD dropped below that concentration. In addition, the higher $C_{min,ss}$ and trough values for the Cardizem CD treatments lead to less daily fluctuation in the plasma diltiazem concentrations. This is illustrated by a lower RATIO ($C_{max,ss}/C_{min,ss}$) value for subjects treated with Cardizem CD compared to Dilacor XR.

Also important is the increased variability (%CV) within the Dilacor XR treatments compared to the Cardizem CD treatments. Figure 5 compares the variability of the plasma diltiazem concentrations between Dilacor XR and Cardizem CD at the $180\,mg\,d^{-1}$ dose level for selected time points on day 7. One reason for the variability in the Dilacor XR dosage form performance may be the difference in the delivery systems of the two formulations. Cardizem CD is a beaded product while Dilacor XR is a swellable polymeric matrix core delivery system.[13]

These data suggest that indiscriminate switching between Dilacor XR and Cardizem CD is not advisable in patients already established on a particular dosage form.

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