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THE INFLUENCE OF TIME OF ADMINISTRATION ON THE PHARMACOKINETICS OF A ONCE-A-DAY DILTIAZEM FORMULATION: MORNING AGAINST BEDTIME

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ABSTRACT

Twenty-three young, healthy, male volunteers received, in a randomized crossover design, 240 mg of a once-a-day diltiazem formulation at 08:00 (AM) or 22:00 (HS) for 6 days. A 7 day washout period was observed between the two modes of administration. Diltiazem plasma concentrations were monitored every hour for 24 h and at 30, 36, and 48 h after the last dose. Differences were found between AM and HS dosing for C_{min} (mean (SD) = 47·2 (25·8) against 39·6 (21·1) ng mL^{-1}, $p = 0{\cdot}038$), AUC_{0-24} (2008 (814) against 1754 (714) ng h mL^{-1}, $p = 0{\cdot}024$), and AUC_{0-48} (2662 (1244) against 2395 (238) ng h mL^{-1}, $p = 0{\cdot}034$). Overall the two modes of administration did not produce bioequivalent pharmacokinetic profiles. Also HS dosing gave significantly higher plasma concentrations of diltiazem in the early morning hours when the incidence of cardiovascular events is higher. If one assumes a strong correlation between plasma concentrations and myocardial protection then HS dosing should be recommended for QD formulation of diltiazem. Clinical studies should be performed to confirm this theoretical pharmacokinetic advantage.

KEY WORDS: diltiazem; pharmacokinetics; circadian rhythm; chronopharmacology

INTRODUCTION

Circadian variations in the pharmacokinetics of many drugs have been reported over recent years.[1] Some cardiovascular drugs, such as propranolol[2] and nitrates[3,4] exhibit changes in their pharmacokinetics depending on the time of the day chosen for their administration.

Calcium channel blockers also display such chronokinetic variability. Studies using the dihydropyridine drugs nifedipine[5] and nicardipine[6] and the

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phenylalkylamine drug verapamil[7,8] showed a constant trend for higher maximal plasma concentration (C_{max}) and areas under the curve (AUC) values when given in the morning (AM) rather than in the evening or at night. Diltiazem, a benzothiazepine drug, displayed a similar pharmacokinetic profile when given at a dose of 60 mg four times a day.[9] All these studies were carried out using plain-release formulations of the drugs. One chronokinetic study with verapamil involving the slow-release formulation gave discrepant results compared with its plain-release formulation, AUC being significantly higher after evening dosing than after AM dosing.[10]

Actually, temporal fluctuations throughout the day of some physiological functions regulating the bioavailability of a drug through (i) absorption (gastric emptying,[11] intestinal transit,[12] gastrointestinal pH[13]), (ii) distribution (plasma protein concentrations[14]), (iii) metabolism (hepatic blood flow,[15] enzymatic activities[16]) and excretion (urinary pH,[17] glomerular filtration rate[18]) have been described in animals and humans.

Chronokinetics of slow-release formulations has become increasingly important since formulations allowing once-a-day (QD) dosing have become more popular. Compared with drugs that must be taken two to four times a day, QD formulations can be taken any time during the day in the absence of relevant information on the diurnal variation of their pharmacokinetics and/or pharmacodynamics. This large flexibility in dosing time can be problematic if a drug presents different pharmacokinetic profiles for different administration times, and if there is a relation between these profiles and the therapeutic or toxic response.

On the other hand, large epidemiological and clinical studies have reported that myocardial infarctions[19,20] and angina attacks[21,22] are significantly more frequent in the morning hours (06:00–noon) than at any other time of the day. When rising time is taken into consideration, the data confirmed that these cardiovascular events occur more frequently in the 4 h that follow rising.[23] These critical hours can be explained in part by: (i) a sharp rise in systemic arterial pressure,[24,25] (ii) an increase in coronary vascular tone,[26] (iii) a circadian peak of platelet aggregability,[27] (iv) a circadian trough of fibrinolytic activity,[28] and (v) a circadian peak of blood viscosity.[29] The synchronicity of these mechanisms in a short time span could result in a largely increased risk of developing coronary events.

The main objective of the present study was to evaluate whether QD diltiazem 240 mg taken AM at 08:00 or at bedtime (HS) at 22:00 has the same pharmacokinetic profile at steady state in healthy volunteers. The secondary objective was to compare diltiazem plasma concentrations at each hourly blood sampling time during a 04:00 to 08:00 critical period.

PARTICIPANTS AND METHODS

This was a randomized, open label, two-way-balanced, crossover trial approved by the ethics committee of Maisonneuve-Rosemont Hospital.

Twenty-four participants were enrolled. The participation of one was discontinued after the first period because of inaccurate drug intake. The 23 other participants completed the trial. They were all healthy, Caucasian, male volunteers with mean (SD) age of 25·9 (5·3) years, height of 176·8 (6·7) cm, and weight of 78·1 (7·2) kg. They had all been non-smokers for at least 1 year and gave informed consent prior to their entry into the study. None of them had been working on night shifts or had had irregular sleep patterns during the previous month. They were asked to maintain regular eating, sleeping, and lifestyle habits throughout the study. No concomitant medications were permitted.

Participants were randomly assigned to either group A or group B. In order to reach steady state, participants in both groups took QD diltiazem 240 mg (Cardizem-CD®) at home for 5 d at 08:00 (group A) or 22:00 (group B). Each time they took the study drug at home they called the study coordinator who recorded the compliance. They came to the hospital on the evening of day 5 and took their sixth and last dose on day 6, either at 08:00 with 250 mL of water and prior to a standardized breakfast (group A) or at bedtime with 250 mL of water (group B). While in the hospital, food, liquids, and sleeping time were standardized (Figure 2). Daytime activities were minimal and participants were not allowed to lie down from 08:00 to 22:00 hours. After a 7 d washout period, both groups underwent the same procedure again but at the alternate dosing time.

Blood sampling was done prior to and every hour for the first 24 h and at 30, 36, and 48 h after the sixth dose. Blood was taken by direct venous punctures in daytime but, to minimize sleep disturbances, a catheter was installed for overnight sampling. Blood was collected in EDTA Vacutainer® tubes and plasma was assayed by high-performance liquid chromatography for diltiazem, *N*-desmethyldiltiazem (MA), and desacetyldiltiazem (DAD) according to the method of Caillé *et al.*[30] The limit of quantification for diltiazem, MA, and DAD was 5 ng mL^{-1} for each.

Participants were asked to empty their bladder prior to the sixth dose and to specifically collect urine from 0 to 10 and 10 to 24 h after dosing, periods during which individual urine volumes were pooled. Urine samples were taken for further assay of diltiazem by high-pressure liquid chromatography, according to the method published by Tawashi *et al.*[31]

The following primary pharmacokinetic parameters were observed or derived from diltiazem plasma concentrations: C_{max}, C_{min}, AUC_{0-24}, and AUC_{0-48}. C_{max} and C_{min} were the observed values of respectively maximal and minimal diltiazem plasma concentrations in the 0–24 h interval. The AUCs were estimated by the trapezoidal method. The following secondary pharmacokinetic parameters were also computed or observed: terminal elimination half-life ($t_{1/2}$), $AUC_{0-\infty}$, time of C_{max} (t_{max}), time of C_{min} (t_{min}), and fluctuation index. Elimination rate constant (k_{el}) was estimated by non-linear least-squares regression and $t_{1/2}$ was obtained by equation $\ln(2)/k_{el}$.

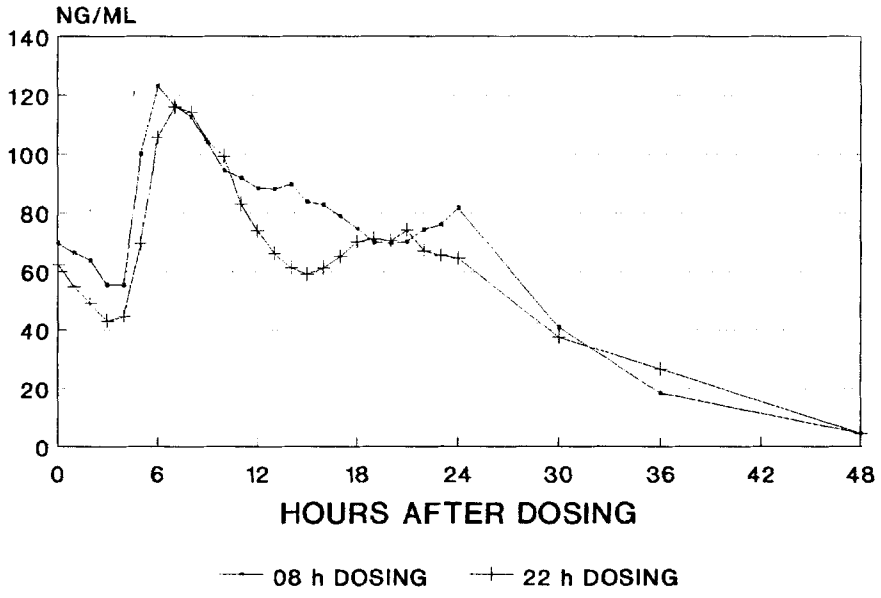

Figure 1. Mean diltiazem plasma concentration against time after the last dose at steady state

$AUC_{0-\infty}$ was computed by adding the ratio of the last quantifiable diltiazem plasma concentration divided by k_{el} to AUC_{0-48}. The fluctuation index between C_{max} and C_{min} was calculated using the following formula: $((C_{max}-C_{min})/(AUC_{0-24}/24)) \times 100$.

Statistical analysis was done by an ANOVA test for repeated measurements. Bioequivalencee for the two study regimens was evaluated by the 90% confidence interval of the ratio of HS/AM for C_{max}, C_{min}, AUC_{0-24}, and AUC_{0-48} after logarithmic transformation. Bioequivalence was rejected if the 90% confidence interval of the ratio was outside the range 0·80–1·25 with respect to AUC_{0-24}, AUC_{0-48}, C_{max}, or C_{min}.

RESULTS

Figure 1 presents the mean diltiazem plasma concentration against experimental time curves obtained after 08:00 and 22:00 administrations. After ingestion of study drug, a lag time of approximately 4 h is observed and C_{min} occurs at the end of this lag time. A second peak in mean C_p is observed near the end of the dosing interval.

Mean steady state pharmacokinetics of diltiazem with this QD formulation are presented in Table 1, that shows statistically significant differences ($p<0·05$) between the two dosing schedules for AUC_{0-24}, AUC_{0-48}, and C_{min}.

Table 1. Mean ± SD steady state pharmacokinetic parameters

	08:00 dosing	22:00 dosing	p
Primary parameters			
AUC_{0-24} (ng h mL^{-1})	2007·74 ± 814·18	1753·65 ± 714·68	0·024
AUC_{0-48} (ng h mL^{-1})	2662·02 ± 1244·20	2394·57 ± 237·55	0·034
C_{max} (ng mL^{-1})	137·7 ± 48·6	127·6 ± 47·8	0·188
C_{min} (ng mL^{-1})	47·2 ± 25·8	39·6 ± 21·1	0·038
Secondary parameters			
$t_{1/2}$ (h)	7·14 ± 1·23	7·95 ± 1·39	0·063
$AUC_{0-\infty}$ (ng h mL^{-1})	2764·5 ± 1266·4	2541·4 ± 1155·3	0·094
t_{max} (h)	8·9 ± 5·3	6·8 ± 1·1	0·076
t_{min} (h)	9·7 ± 8·5	7·3 ± 7·5	0·340
Fluctuation index (%)	112·5 ± 25·5	125·8 ± 31·2	0·058

Table 2. Bioequivalence parameters of AM and HS administration of QD diltiazem

	AUC_{0-24}	AUC_{0-48}	C_{max}	C_{min}
Lower bound	0·784	0·814	0·817	0·697
Mean ratio	0·865	0·887	0·914	0·835
Upper bound	0·954	0·967	1·021	1·000

Table 2 presents the results of bioequivalence assessment and shows that both AUC_{0-24} and C_{min} fall under the 0·80 lower limit of the 90% confidence interval while AUC_{0-48} and C_{max} remain within the limits.

Diltiazem plasma concentrations can also be plotted on a real time axis to obtain a 'chronokinetic' profile. Such curves are presented in Figure 2. One can see from that figure that the two schedules of administration result in very different hourly concentrations. Qualitatively, mean plasma concentrations after AM dosing reach C_{min} near 11:00 and C_{max} around 14:00 while the second peak is observed near 07:00. On the other hand, HS administration results in mean concentrations presenting C_{min} near 01:30, C_{max} near 05:30 and the second peak near 19:00.

The mean (SD) amounts of diltiazem recovered in urine during the first 10 h after dosing time are not statistically different for the AM and the HS administrations (1898·7 (1026) against 2129·1 (1703) mcg respectively, $p = 0·592$). However, mean (SD) amounts recovered in the 14 h that followed are almost two times greater after AM dosing than after HS dosing (3797·9 (1888) against 1967·9 (1145) mcg respectively, $p < 0·001$).

The mean plasma concentration–time curves of MA and DAD are shown in Figure 3. MA has a pharmacokinetic profile qualitatively similar to diltiazem. AM dosing gave higher mean peaks and troughs than HS dosing. However

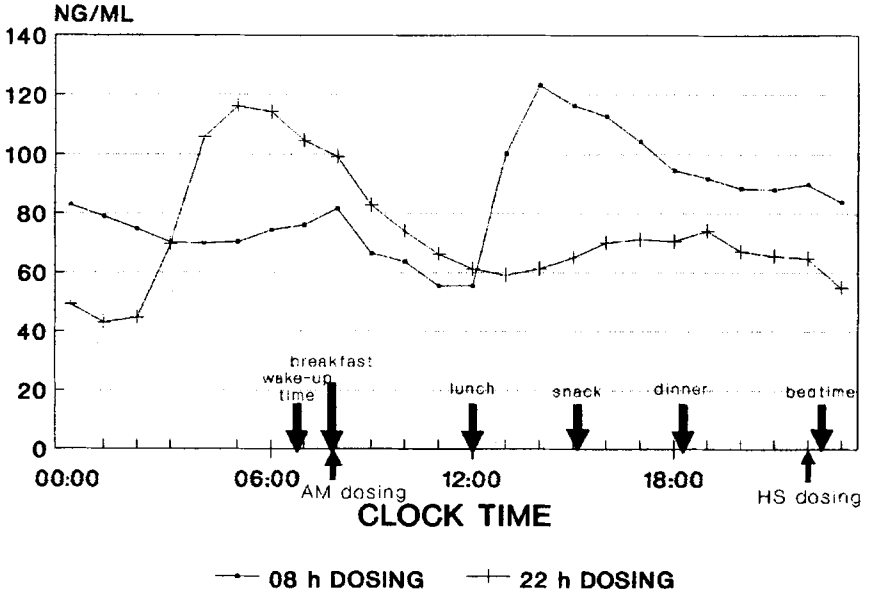

Figure 2. Mean diltiazem plasma concentration against clock time at steady state over the dosing interval

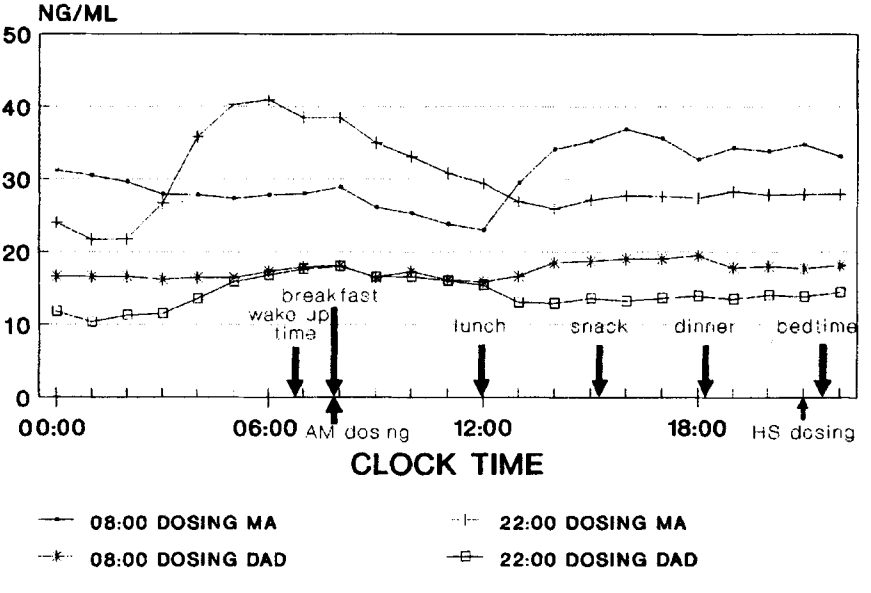

Figure 3. Mean MA and DAD plasma concentrations against clock time after the last dose at steady state

Table 3. Mean ± SD diltiazem plasma concentration between 04:00 and 08:00 hours

Hour	08:00 admin. (ng mL^{-1})	22:00 admin. (ng mL^{-1})	Level of significance
04:00	69·8	105·7	$p<0·000\ 01$
05:00	70·2	116·1	$p<0·000\ 01$
06:00	74·4	114·3	$p<0·000\ 01$
07:00	76·1	104·7	$p<0·000\ 25$
08:00	81·7	99·3	$p=0·017$

mean (SD) AUCs for both the 0–24 and 0–48 h intervals are not significantly different between AM and HS administrations (885·1 (171·5) against 849·3 (212·7) ng h mL^{-1}, $p=0·2599$ and 1050·1 (338·2) against 1021·6 (378·3) ng h mL^{-1}, $p=0·4659$, respectively).

DAD has a qualitatively different kinetic profile from diltiazem and from MA. HS dosing results in lower mean DAD plasma concentrations than AM dosing. Mean AUCs for the 0–24 and 0–48 h intervals for the two dosing times are significantly different (417·4 (484·4) against 340·4 (381·2) ng h mL^{-1}, $p=0·0379$ and 450·5 (537·2) against 368·4 (420·8) ng h mL^{-1}, $p=0·0376$, respectively).

Hourly diltiazem concentrations obtained from the two dosing schedules are also very different during the 04:00–08:00 morning period critical for coronary events. AM administration of QD diltiazem results in significantly lower plasma levels during this critical period than HS administration (Table 3).

DISCUSSION

It is interesting to observe that the difference in HS/AM relative bioavailability tends to decrease with time after dosing, $F_{0-24}<F_{0-48}<F_{0-\infty}$. It is unlikely that absorption persists over 48 h, therefore a slower clearance rate for AM in the first hours after dosing may be foreseen. This is not, however, explained either by urinary recovery, which may be considered negligible since less than 6 mg is recovered in urine as unchanged diltiazem in 24 h, or by biotransformation of diltiazem into MA or DAD.

Moreover, this difference is so significant that morning and bedtime administration of QD diltiazem are not bioequivalent. Morning administration results in significantly higher C_{min}, AUC_{0-24}, and AUC_{0-48}. This lack of bioequivalence further confirms the difference in bioavailability with respect to the two moments of administration.

The pharmacokinetic profile of QD diltiazem formulation used in this study presents two peaks. The reason for the second of the two peaks is obscure. It is

unlikely to be caused by enterohepatic recirculation since this second peak is not seen with the IV formulation.[32] This second peak is seen around 20 h after dosing, when the remaining tablet is likely to be deep into the colon, and happens on day 7 slightly after dinner for HS administration or after breakfast for AM administration. One may then consider the influence of an increased peristaltism induced by the meal that enhances tablet disintegration and diltiazem release, dissolution, and absorption.

The result of Table 3 could be significant in therapeutics considering the special pharmacological protection needed by patients during this time interval. If one assumes a correlation between diltiazem plasma levels and efficacy in preventing coronary events such as angina attacks and myocardial infarction, then bedtime administration of diltiazem QD should be recommended. A clinical trial should, however, be performed to verify whether this pharmacokinetic difference translates into a clinically significant one.

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