REPERCUSSION OF THE FORMULATION ON DILTIAZEM PHARMACOKINETICS IN HEALTHY VOLUNTEERS

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To be submitted to Clinical Drug Investigation
ABSTRACT

Goals: Given that the ability of the small intestine to biotransform a drug may decrease in distal segments of the intestine, this study was conducted to determine the impact of modified-release preparations on diltiazem bioavailability.

Methods: Two trials were undertaken with 18 healthy volunteers in each protocol. Volunteers received, in a randomized cross-over design, diltiazem tablets (T) 60 mg q 6 hr and diltiazem SR (twice-a-day modified-release formulation) 120 mg q 12 hr for 4 days, with a 10-day washout period prior to cross-over. The second trial had an identical study design except for the treatments, which consisted of diltiazem tablets 60 mg q 6 hr and diltiazem CD (once-a-day modified-release formulation) 240 mg die. Blood samples were drawn hourly for the first 24 hrs, every 2 hrs for the next 24 hrs and once at the end of days 3 and 4. Diltiazem and its metabolites, N-desmethyldiltiazem (MA) and desacetyldiltiazem (M1), were assayed in plasma by HPLC.

Results: Compared with tablets, diltiazem AUC$_{0-96\text{hrs}}$ was decreased with both modified-release formulations, i.e. 8353 ± 439 vs 9157 ± 149 ng.h/ml (SR vs T) (p<0.05) and 6124 ± 526 vs 8736 ± 657 ng.h/ml (CD vs T) (p<0.05). The AUC$_{0-96\text{hrs}}$ of MA was also decreased following the administration of modified-release formulations, i.e. 3465 ± 118 vs 3761 ± 115 ng.h/ml (SR vs T) (p<0.05) and 2191 ± 146 vs 3266 ± 195 ng.h/ml (CD vs T) (p<0.05), whereas the AUC$_{0-96\text{hrs}}$ of M1 was not affected by the different formulations. Relative to the tablet formulation, diltiazem bioavailability decreased with the SR and the CD formulations, i.e. 92±3% and 71±4% respectively.
Conclusions: Diltiazem bioavailability decreased with the administration of modified-release preparations, most likely due to a slower or an incomplete drug release and to the involvement of countertransport mechanisms in the gut mucosa.
INTRODUCTION

Diltiazem, a calcium channel blocker belonging to the benzothiazepine family, is widely prescribed for the treatment of hypertension and angina (1). Given its physico-chemical properties, diltiazem undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A (2), which results in less than 4% of its oral dose being excreted unchanged in urine (3,4).

Diltiazem bioavailability is approximately 30 to 40% due to an important first-pass metabolism (1,3,4). The amount of diltiazem reaching the systemic circulation shows a great interindividual variability, which may range from 24 to 74% (3-6). The first-pass metabolism of a drug given orally may occur within three potentially active metabolic sites, i.e. the intestine, the liver and the lungs. Even though the liver has been acknowledged as the major site of drug biotransformation, we have demonstrated, in the rabbit, that diltiazem is also metabolized in the intestine (7-9). Intestinal metabolism of diltiazem is qualitatively similar to the hepatic disposition pathways, but appears to be site-dependent. In the rabbit, due to a lower metabolic capacity in the distal intestine, diltiazem bioavailability is increased following its administration in distal intestinal segments compared with its injection in proximal segments of the intestine (7,8).

The short half-life of diltiazem ranging from 3.5 to 6 hours (3,4) requires multiple daily drug dosage in order to maintain adequate plasma concentrations. Hence, modified-release formulations are used clinically as once-a-day (diltiazem CD) or twice-a-day (diltiazem SR) preparations (1). These formulations, for the most part, release a small
amount of diltiazem upon intake and release the rest steadily throughout the gut over the
dosing interval. Therefore, distal regions of the gut are exposed to concentrations of
xenobiotics higher than what could be expected following the administration of an
immediate-release formulation. The effect of different release rates on diltiazem
bioavailability is still controversial due to the presence of conflicting reports on the
bioequivalence of diltiazem administered in different formulations (5,10-13). This study
was undertaken to assess whether the administration of diltiazem in modified-release
formulations would result in a greater bioavailability than when administered in an
immediate release preparation, as it has been described for nisoldipine coat-core tablet
formulation (14).
MATERIAL AND METHODS

Given the amount of blood sampling required to assay diltiazem and its metabolites, two separate groups of healthy volunteers were recruited in each study. Study design was a randomized, open label, two-way balanced cross-over trial conducted in one clinical site (Maisonneuve-Rosemont Hospital, Montréal, Canada). Following the approval of the protocols by the Ethics Committee, informed consent was obtained once the purpose, procedures and risks of the study were explained to the volunteers. Demographics are summarized in Table 1 for the two consecutive trials.

All participants had normal medical, biochemical and haematological profiles as documented by blood chemical tests performed within 30 days of study entry. Volunteers were non-smokers or ex-smokers for at least one year and had to be within 15% of their average body weight. None of the participants had experienced previous cardiovascular disorders, hepatic, renal, endocrine and/or haematological diseases. All participants had a pulse rate over 45 bpm, a systolic blood pressure (SBP) over 90 and under 160 mmHg, a diastolic blood pressure (DBP) under 95 mmHg and absence of any AV blockage. In both studies, the lower limit for a first-degree AV block was set at 225 ms. Volunteers were not allowed to donate blood or to take part in any other clinical study within 30 days prior to the trial.
Commercially available formulations were used in this study in order to deliver diltiazem at different sites within the gastro-intestinal tract. Effectively, as diltiazem tablets tend to release their content rapidly in the intestinal lumen, the majority of the drug is delivered in the upper segments of the intestinal tract. On the other hand, through coating of its beads, modified release diltiazem formulations tend to release their content throughout their respective dosing interval, i.e. 12 hours for diltiazem SR and 24 hours for diltiazem CD.

Volunteers were admitted to the clinical unit on the night preceding the trial. Eighteen healthy volunteers were recruited and completed Study 1. Participants fasted for 8 hours before each period and then, they randomly received either diltiazem tablets (Cardizem® 60 mg tablets four times daily (06:00h, 12:00h, 18:00h and 00:00h) (Lot # 2073, Hoechst Marion Roussel Canada Inc.), or diltiazem SR (Cardizem® SR) 120 mg capsules twice daily (06:00h and 18:00h) (Lot # 2085, Hoechst Marion Roussel Canada Inc.) over four days. Following a 10-day washout period, participants received the alternate treatment. Participants remained on the hospital ward for the first 48 hours following administration. Once discharged, they had to confirm their drug intake by telephone contacts for the remaining 48 hours.

To characterize diltiazem disposition, blood samples were drawn over the 4-day period; i.e. prior to drug administration, every half hour for the first 4 hours and hourly blood collection for the first 24 hours. On day 2, blood samples were drawn every second hour. One sample was drawn at the end of day 3 and day 4, i.e. at 72 and at 96
hrs post drug intake. Total blood volume collected over the study duration did not exceed 900 mL.

Study 2 was undertaken in the same clinical facility with eighteen new participants (Table 1) according to the above-mentioned inclusion/exclusion criteria. Participants underwent the same procedures as described earlier. Upon admission to the clinical unit, they randomly received either diltiazem tablets (Cardizem®) 60 mg tablets four times daily (06:00h, 12:00h, 18:00h and 00:00h) (Lot # 2073, Hoechst Marion Roussel Canada Inc.), or diltiazem CD (Cardizem® CD) 240 mg capsules once daily (06:00h) (Lot # 2076, Hoechst Marion Roussel Canada Inc.) over a four day period. After the 10-day washout period, participants crossed-over to the alternate treatment. With the exception of the half-hourly blood draws, blood sampling was performed at the same intervals as described in study 1. Total blood volume collected over the study duration did not exceed 820 mL.

Blood samples were immediately centrifuged (2500xg, 10 min), and the plasma was kept frozen at -20°C until assay. Plasma concentrations of diltiazem and of its two major metabolites, N-desmethyldiltiazem (MA) and desacetyldiltiazem (M1), were assayed by HPLC as described previously (15). The lower limit of detection was 2.5 ng/mL.
Pharmacokinetic parameters

Initial kinetic parameters were determined by graphic analysis as described by Gibaldi and Perrier (16). The areas under the curve of plasma concentrations of diltiazem, MA and M1 as a function of time (AUC0-96h) were estimated by means of the trapezoidal method. The percentage of the metabolites AUC relative to that of diltiazem were calculated as follows, (AUC_{METABOLITE(0-96)}/AUC_{DTZ(0-96)}) *100%. The maximum plasma concentration (Cmax), the time to reach maximum plasma concentration (tmax) and the pre-dose concentration (Cpd) were estimated from the data of the first two days and daily trough concentrations afterwards.

In this study, the relative bioavailability was determined by comparing the mean AUC of the tested formulations (diltiazem SR or diltiazem CD) to that of the reference formulation (diltiazem tablets), according to the following equation:

\[ F = \frac{AUC_{(SR \ or \ CD) \ (0-96)}}{AUC_{(TABLETS) \ (0-96)}} \times 100\% \]

The time to reach (TTR) diltiazem plasma concentration of 60 ng/mL and the time to maintain (TTM) this plasma level were reported. The 60 ng/mL minimal effective plasma concentration of diltiazem was selected based on previously published references (17-19).

Statistical analysis

The results are presented as the mean ± S.E.M. Differences between each group were assessed using one-way analysis of variance for repeated measurements, and the
significance was determined using Dunnett's distribution tables. The minimal level of significance was established at p<0.05. Due to the small sampling in both trials, only descriptive statistics were performed on the incidence of adverse events.
RESULTS

Trial 1

The eighteen volunteers enrolled completed the protocol and were included in the pharmacokinetic analyses. There were no differences in the incidence or the severity of adverse events between study treatments and none prompted discontinuation of study treatments.

Mean area under the curve plasma concentrations of diltiazem was lower following the administration of a twice-a-day sustained-release formulation compared to the immediate-release values. This was mainly due to lower diltiazem plasma levels during the first two days, as reflected by a smaller AUC$_{0-24}$ for study days 1 and 2 (Table II). In the group given the sustained-release formulation, diltiazem $C_{\text{max}}$ and concentration pre-dosing ($C_{\text{pd}}$) were smaller on the first day only. At the end of the second study day, diltiazem SR plasma levels were similar to those observed with diltiazem tablets (Table II and Figure 1). Diltiazem bioavailability following the administration of diltiazem SR relative to that of the tablet formulation was estimated at 92 ± 3% (Table II).

In the group who received diltiazem SR, mean AUC$_{0-96\text{hrs}}$ and $C_{\text{max}}$ of N-desmethyldiltiazem (MA) plasma concentrations were lower throughout the study period as compared to values documented with the immediate release formulation (Table II and Figure 2). On the other hand, M1 plasma levels were not affected by the formulations (Figure 3). Mean M1 AUC$_{0-96\text{h}}$ values and $C_{\text{max}}$ values remained similar between both
groups with the exception of an initial smaller \( \text{AUC}_{0-24} \) during the first day.

**Trial 2**

Seventeen subjects completed the study and were included in the pharmacokinetic analyses. There were no differences in the incidence or the severity of adverse events between study treatments, although one participant elected to discontinue due to adverse events during the second period.

Consistent with the previous results, the administration of diltiazem CD generated smaller mean \( \text{AUC}_{0-96\text{hrs}} \), \( \text{C}_{\text{max}} \) and \( \text{Cpd} \) of diltiazem plasma concentrations throughout the trial, compared to the administration of diltiazem tablets (Table III, Figures 4,5). The bioavailability of diltiazem CD relative to diltiazem tablets was estimated at \( 71 \pm 4\% \) (Table III).

Following the administration of diltiazem CD, mean values of MA \( \text{AUC}_{0-96\text{hrs}} \) and \( \text{C}_{\text{max}} \) were lower throughout the trial than respective values observed with diltiazem tablets (Table III, Figure 5). On the other hand, M1 plasma levels were not affected by the different formulations (Figure 6). This is reflected in mean M1 \( \text{AUC}_{0-96\text{th}} \) values and \( \text{C}_{\text{max}} \) values, which were not modified between both groups with the exception of a transient decrease in \( \text{AUC}_{0-24} \) during the first day (Table III). The percentage of M1 area under the curve relative to that of diltiazem tended to increase (\( p=0.0576 \)) with the once-a-day formulation as compared to the immediate release group (Table III).
DISCUSSION

In humans, the amount of cytochrome P450 and of other enzymes known to metabolize diltiazem have been reported to decrease in distal intestinal segments (20,21), and as a consequence, the first-pass metabolism of some drugs should be reduced. Confirming this hypothesis, diltiazem area under the curve was greater following the administration of diltiazem SR than the AUC estimated following the intake of the tablet formulation (11). In the present study, however, the area under the curve of plasma concentrations of diltiazem in healthy volunteers did not increase following the administration of the modified-release formulations, diltiazem SR or diltiazem CD. The observed decrease in diltiazem bioavailability does not confirm previously published results in humans (10-13) and in animals (8). The present results are not an exception, since it has been documented that relative to an immediate release formulation, modified-release formulations reduce the bioavailability of nicardipine (22), nifedipine (23), propranolol (24) and morphine (25).

In animals, we have demonstrated that the delivery of diltiazem into distal segments of the intestine of rabbits, where in vitro metabolic activity is diminished (7), increases its systemic availability (8). Aside from the obvious inter-species differences between rabbits and humans, the observed discrepancy with the animal data could most likely be explained by the different methodological procedures employed. Effectively, in animals, a solution of diltiazem was injected into targeted intestinal segments identified under laparotomy (8), whereas in this study, diltiazem formulations with varying release rates were administered to mimic proximal and distal drug delivery.
Given the length of the trials, steady-state was most likely reached with all formulations, as reflected in diltiazem plasma concentrations at trough. Hence, other possibilities can contribute to the discrepancy between our results and the animal data. The observed decrease in diltiazem bioavailability with modified-release formulations could theoretically be explained by an increase in the first-pass metabolism or by a decrease in the amount of drug absorbed. Diltiazem undergoes biotransformation via multiple pathways of N-oxidation, N-desmethylation, O-deacetylation and conjugation (26), known to be inhibited by diltiazem itself and by MA (27). Inhibition or saturation of each of the enzymatic reactions might occur with immediate-release formulations as enzymes are exposed to larger amounts of drug, compared to a slower input from modified-release preparations, as described for diltiazem, nifedipine and verapamil (5,28). A higher amount of diltiazem may partially escape the first-pass metabolism and thus, achieve a higher bioavailability with immediate-release preparations (5,6). In the present study, however, the fact that the ratios of MA and M1 AUC to diltiazem AUC remained unchanged following the administration of the SR and CD formulations strongly suggests that the formulations at the doses used did not change the first-pass metabolism of diltiazem. Furthermore, another study comparing the kinetics of 120 mg of diltiazem twice daily to 240 mg of diltiazem once daily did not report any differences between the areas under the curves (13), also suggesting that the rate of input of diltiazem at 240 mg may have little influence on its first-pass metabolism.
Hence, the most likely explanation for the decrease in diltiazem bioavailability with the modified-release preparations is decreased drug absorption. Such a decrease in absorption could theoretically result from bypassing intestinal active absorption sites, changes in the luminal pH affecting diltiazem dissolution, changes to the gastro-intestinal transit time, a slower or an incomplete drug release and implication of a counter-transport process via intestinal p-glycoprotein. Under our experimental conditions, most of these variables are not applicable since diltiazem is well absorbed throughout the gut by passive diffusion (1,6) and as the dissolution of the formulations used here is not pH-dependent (29). Furthermore, the crossover design of the studies offsets any impact changes to the gastro-intestinal transit times might have on drug absorption.

P-glycoprotein acts as an ATP-dependent drug efflux pump to transport from the cytosol into the lumen of cytotoxic and commonly used drugs, including diltiazem. While p-glycoprotein is expressed in a variety of tissues, high levels are reported on the apical surface of adrenal cortex, hepatocytes, in the small intestine and particularly in the colon (30). Recently, Benet et al. (1996) suggested that p-glycoprotein could play an important role in reducing the bioavailability of certain compounds via antitransport processes. Given the fact that diltiazem is a substrate of p-glycoprotein and given their higher content in the colon, we can assume that the decreased bioavailability with modified-release formulations of diltiazem especially in the colon is somewhat linked to p-glycoprotein (30-33).
The diltiazem modified-release preparations used in this study appear to release their entire active ingredient within the prescribed time frame, as supported by \textit{in vitro} dissolution studies (29). We must therefore contemplate the possibility that our results are secondary to an incomplete absorption of the drug due to either the involvement of \textit{p}-glycoproteins or to the possibility that the modified release formulation might have been eliminated in the faeces prior to the complete release of its content. We cannot confirm such hypotheses given that diltiazem was not assayed in the volunteers’ faeces. Consistent with our explanation, the reduced bioavailability of propranolol and morphine modified release formulations were reported to be secondary to a reduction in the amount of absorbed drug (24,25).
In summary, this study reports a decreased bioavailability of diltiazem when administered in modified-release preparations compared to the immediate-release formulation in healthy volunteers. A slower or an incomplete drug release combined with the involvement of p-glycoproteins appear to be the most likely explanation for the decreased bioavailability.
REFERENCES


31. Benet LZ, Wu CY, Hebert MF and Wacher VJ. Intestinal drug metabolism and


Table I: Participant demographics.

<table>
<thead>
<tr>
<th></th>
<th>Age (years) mean (range)</th>
<th>Height (cm) mean ± SD</th>
<th>Weight (kg) mean ± SD</th>
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<tr>
<td><strong>Study 1</strong></td>
<td>26 (19-34)</td>
<td>177 ± 5</td>
<td>75.4 ± 6.1</td>
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<td>N = 18 men</td>
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<tr>
<td><strong>Study 2</strong></td>
<td>27 (19-41)</td>
<td>179 ± 6</td>
<td>79.6 ± 6.2</td>
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<tr>
<td>N = 18 men</td>
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Table II: Diltiazem pharmacokinetic parameters following the daily administration of an immediate-release formulation (60 mg QID) and a sustained-release formulation (120 mg BID) to healthy volunteers for 4 consecutive days (N=18).

<table>
<thead>
<tr>
<th></th>
<th>60 mg QID</th>
<th>120 mg BID</th>
<th>60 mg QID</th>
<th>120 mg BID</th>
<th>60 mg QID</th>
<th>120 mg BID</th>
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<tr>
<td>AUC_{DAY1} (ng.h/mL)</td>
<td>1572 ± 72</td>
<td>1248 ± 69</td>
<td>612 ± 16</td>
<td>509 ± 17</td>
<td>163 ± 10</td>
<td>135 ± 14</td>
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<td>AUC_{DAY2} (ng.h/mL)</td>
<td>2602 ± 126</td>
<td>2256 ± 109</td>
<td>1011 ± 26</td>
<td>903 ± 29</td>
<td>378 ± 25</td>
<td>334 ± 35</td>
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<td>AUC_{DAY3} (ng.h/mL)</td>
<td>2439 ± 147</td>
<td>2373 ± 144</td>
<td>1047 ± 37</td>
<td>1006 ± 40</td>
<td>407 ± 42</td>
<td>413 ± 44</td>
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<td>AUC_{DAY4} (ng.h/mL)</td>
<td>2544 ± 149</td>
<td>2476 ± 163</td>
<td>1091 ± 42</td>
<td>1047 ± 44</td>
<td>445 ± 55</td>
<td>454 ± 52</td>
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<tr>
<td>AUC_{0-96hrs} (ng.h/mL)</td>
<td>9157 ± 149</td>
<td>8353 ± 439</td>
<td>3761 ± 115</td>
<td>3465 ± 118</td>
<td>1392 ± 126</td>
<td>1337 ± 143</td>
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<td>% MA/DTZ AUC_{(0-96)}</td>
<td>42 ± 2</td>
<td>43 ± 1</td>
<td>16 ± 2</td>
<td>17 ± 2</td>
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<tr>
<td>% M1/DTZ AUC_{(0-96)}</td>
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<tr>
<td>Cmax_{DAY1} (ng/mL)</td>
<td>123 ± 6</td>
<td>105 ± 6</td>
<td>42 ± 1</td>
<td>37 ± 1</td>
<td>14 ± 1</td>
<td>12 ± 1</td>
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<td>Cmax_{DAY2} (ng/mL)</td>
<td>159 ± 7</td>
<td>143 ± 8</td>
<td>52 ± 1</td>
<td>47 ± 2</td>
<td>24 ± 5</td>
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<td>Tmax_{DAY1} (hr)</td>
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<td>Tmax_{DAY2} (hr)</td>
<td>32 ± 1</td>
<td>35 ± 2</td>
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<tr>
<td>Cpdm_{DAY2} (ng/mL)</td>
<td>76 ± 18</td>
<td>68 ± 17</td>
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<td>Cpdm_{DAY3} (ng/mL)</td>
<td>95 ± 25</td>
<td>96 ± 25</td>
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<td>TTR (hr)</td>
<td>5.8 ± 0.9</td>
<td>9.1 ± 4.8</td>
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<td>TTM (hr)</td>
<td>16.9 ± 1.4</td>
<td>31.2 ± 21.1</td>
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*a. mean ± S.E.M.*

*b. p<0.05 as compared to 60 mg QID values*
Table III: Diltiazem pharmacokinetic parameters following the daily administration of an immediate-release formulation (60 mg QID) and a sustained-release formulation (240 mg DIE) to healthy volunteers for 4 consecutive days (N=17).

<table>
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<tr>
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<th>60 mg QID</th>
<th>240 mg DIE</th>
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<tr>
<td>$AUC_{DAY1}$ (ng.h/mL)</td>
<td>1685 ± 114$^a$</td>
<td>1016 ± 74$^b$</td>
<td>584 ± 27</td>
<td>358 ± 18$^b$</td>
<td>160 ± 22</td>
<td>106 ± 27$^b$</td>
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<tr>
<td>$AUC_{DAY2}$ (ng.h/mL)</td>
<td>2536 ± 164</td>
<td>1867 ± 126$^b$</td>
<td>913 ± 50</td>
<td>650 ± 38$^b$</td>
<td>397 ± 65</td>
<td>384 ± 93</td>
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<tr>
<td>$AUC_{DAY3}$ (ng.h/mL)</td>
<td>2303 ± 209</td>
<td>1672 ± 172$^b$</td>
<td>924 ± 59</td>
<td>634 ± 49$^b$</td>
<td>462 ± 90</td>
<td>479 ± 128</td>
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<td>$AUC_{DAY4}$ (ng.h/mL)</td>
<td>2212 ± 196</td>
<td>1569 ± 187$^b$</td>
<td>846 ± 50</td>
<td>549 ± 51$^b$</td>
<td>487 ± 96</td>
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<td>$AUC_{0-96hrs}$ (ng.h/mL)</td>
<td>8736 ± 657</td>
<td>6124 ± 526$^b$</td>
<td>3266 ± 195</td>
<td>2191 ± 146$^b$</td>
<td>1506 ± 273</td>
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<td>% MA/DTZ $AUC_{(0-96)}$</td>
<td>39 ± 1</td>
<td>37 ± 2</td>
<td>18 ± 3</td>
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<td>% M1/DTZ $AUC_{(0-96)}$</td>
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<td>Cmax$_{DAY1}$ (ng/mL)</td>
<td>126 ± 9</td>
<td>84 ± 5$^b$</td>
<td>40 ± 2</td>
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<td>Cmax$_{DAY2}$ (ng/mL)</td>
<td>161 ± 11</td>
<td>122 ± 9$^b$</td>
<td>51 ± 4</td>
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<td>Tmax$_{DAY1}$ (hr)</td>
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<td>Tmax$_{DAY2}$ (hr)</td>
<td>33 ± 2</td>
<td>32 ± 1</td>
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<tr>
<td>Cpd$_{DAY2}$ (ng/mL)</td>
<td>73 ± 5</td>
<td>55 ± 5$^b$</td>
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<tr>
<td>Cpd$_{DAY3}$ (ng/mL)</td>
<td>95 ± 8</td>
<td>68 ± 7$^b$</td>
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<tr>
<td>TTR (hr)</td>
<td>4.3 ± 0.7</td>
<td>10.1 ± 1.9$^b$</td>
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<tr>
<td>TTM (hr)</td>
<td>16.0 ± 2.2</td>
<td>24.4 ± 2.0$^b$</td>
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*a. mean ± S.E.M.*

*b. p<0.05 as compared to 60 mg QID values.*
Figure 1  
Mean diltiazem plasma concentrations following the administration of a 60-mg immediate-release diltiazem tablet QID (●) and a 120-mg sustained release diltiazem formulation BID (○) in healthy volunteers (N=18)
Figure 2  Mean desmethyldiltiazem (MA) plasma concentrations following the administration of a 60-mg immediate-release diltiazem tablet QID (●) and a 120-mg sustained release diltiazem formulation BID (♦) in healthy volunteers (N=18)
Mean desacetyldiltiazem (M1) plasma concentrations following the administration of a 60-mg immediate-release diltiazem tablet QID (♦) and a 120-mg sustained release diltiazem formulation BID (•) in healthy volunteers (N=18)
Figure 4  Mean diltiazem plasma concentrations following the administration of a 60-mg immediate-release diltiazem tablet QID (●) and a 240-mg sustained release diltiazem formulation daily (●) in healthy volunteers (N=17)
Figure 5  Mean desmethyldiltiazem (MA) plasma concentrations following the administration of a 60-mg immediate-release diltiazem tablet QID (●) and a 240-mg sustained release diltiazem formulation daily (●) in healthy volunteers (N=17)
Figure 6  Mean desacetyldiltiazem (M1) plasma concentrations following the administration of a 60-mg immediate-release diltiazem tablet QID (●) and a 240-mg sustained release diltiazem formulation daily (✦) in healthy volunteers (N=17)