INFLUENCE OF FOOD ON THE BIOAVAILABILITY OF DILTIAZEM AND TWO OF ITS METABOLITES FOLLOWING THE ADMINISTRATION OF CONVENTIONAL TABLETS AND SLOW-RELEASE CAPSULES

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ABSTRACT

The influence of food on the bioavailability of a conventional tablet and of a slow-release capsule of diltiazem was investigated in two separate groups of 24 healthy volunteers in two open crossover studies. Diltiazem, as a conventional tablet (2 x 30 mg, first group) or as a slow-release capsule (120 mg SR, second group), was administered in a fasting condition and 30 min after a breakfast of 784 kcal (23 per cent proteins, 55 per cent lipids, and 22 per cent of carbohydrates). Multiple blood samples were withdrawn during the next 24 h and diltiazem, desmethyldiltiazem, and deacetyldiltiazem were assayed by HPLC. Neither the rate of absorption, assessed by the rate constant of absorption, the peak plasma concentration, and the time required to reach the peak, nor the amount of drug reaching the systemic circulation, assessed by the area under the plasma concentration time curve (AUCm) were influenced by food, and that independently of the formulation. Compared to the fasting experiment, food did not affect either the rate of formation or the AUCm of desmethyldiltiazem or deacetyldiltiazem. The results of the present study show that the relative bioavailability of the single dose of diltiazem administered as a slow-release capsule is significantly higher (69 per cent) than that estimated after the administration of diltiazem in a conventional tablet. It was concluded that food does not influence the bioavailability of diltiazem administered as a conventional tablet or as a slow-release formulation.

KEY WORDS: Diltiazem Tablets Slow-release formulation Bioavailability Food

INTRODUCTION

Diltiazem, a benzothiazepine derivative, is a basic drug rather liposoluble with a partition coefficient of 158. The absorption of diltiazem from the GI tract is
rapid and almost complete. Following its absorption, the drug is rapidly metabolized in the liver with a systemic clearance ranging from 11.5 to 21.3 ml min\(^{-1}\) kg\(^{-1}\). A systemic clearance of that order can be explained on the basis of an elevated intrinsic clearance and a high hepatic extraction ratio. The amount of diltiazem reaching the systemic circulation is approximately 42 per cent of an oral dose, largely due to an important first pass effect. Theoretically, the bioavailability of diltiazem could be modified by factors affecting its absorption or the extent of its first pass.

Several factors may contribute to alter the absorption rate of diltiazem. The formulation is of primary importance, since it has been established that the time required to reach the maximal plasma concentration with aqueous solutions, capsules or tablets is 40, 60, and 180 min, respectively. Age appears also to be of importance; in fact, in the elderly the time to reach the peak plasma concentration after administration of tablets of diltiazem in one study was 300 min. Other factors such as coronary artery disease or sleep have also been shown to delay the absorption of diltiazem.

The amount of diltiazem reaching the systemic circulation after a single dose, shows a great interindividual variability due to its first pass effect. However, the magnitude of the dose does not appear to influence diltiazem bioavailability. Steady state plasma concentrations attained during long-term administration are higher than predicted on single administration, suggesting that hepatic clearance is decreased, possibly entailing a reduction in diltiazem first pass effect.

Food can affect the bioavailability of drugs through different mechanisms: by affecting the rate or the extent of drug absorbed or by modifying the first pass. Theoretically, food could affect the bioavailability of diltiazem by altering any of these parameters. The objective of the present study was to investigate the effect of a standard meal on the bioavailability of a single oral dose of a conventional formulation and of a slow-release preparation of diltiazem.

**METHOD**

*Single dose of a conventional formulation of diltiazem*

A total of 24 male volunteers, randomly allocated into two groups completed the 2-week crossover study. The volunteers were healthy on clinical, haematological, biochemical, and electrocardiographic examination. The participants were non-smokers or had quitted smoking for at least 1 year. They were aged between 18 and 45 (30.7 ± 1.1 years; mean ± SEM) with a mean body weight of 72.0 ± 1.5 kg. The subjects selected had avoided any substance known to influence the activity of the cytochrome P-450 within the month preceding the study and refrained from alcohol or any drug during the week before the study. All subjects signed an informed consent form and fasted overnight before the experimental day. On the experimental day, 12 subjects ingested a standard breakfast half an hour before the intake of two tablets of 30 mg diltiazem (Nordic Laboratories Inc., Kirkland, Québec). The 12 other subjects continued their fasting and were
also given 60 mg of diltiazem. One week later, the two groups received the opposite treatment in order to complete the crossover design. Blood samples were withdrawn from an antecubital vein prior to and at 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 11, 12, 18, and 24 h after the administration of the drug.

**Single dose of a slow-release formulation of diltiazem**

This study was conducted as an open crossover trial. Twenty-four healthy male subjects with a mean ± SEM body weight of 70.4 ± 1.6 kg and a mean age of 24.9 ± 1.1 years were included in this experiment. The criteria of inclusion and exclusion and the experimental conditions were as described above except for the formulation of diltiazem and the blood collection schedule. In this study, the volunteers received a capsule of 120 mg of diltiazem in a slow-release formulation (Cardizem SR 120 mg, Nordic Laboratories Inc., Kirkland, Québec) and blood samples were withdrawn prior to and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 10, 11, 12, 18, and 24 h following drug administration.

For both studies, a standardized breakfast containing 23 per cent proteins, 55 per cent lipids, and 22 per cent carbohydrates, and totaling 784 kcal, was served at 06:30 h to volunteers completing the non-fasting state of the experimentation. At 07:00 h all subjects were administered the drug with 200 ml of water. Standardized lunch and dinner were taken at 12:00 and 18:00 h, respectively. No other food was allowed during the day; however volunteers had free access to liquid after 17:00 h except for caffeinated beverages. Physical activity was limited during the day, especially before lunchtime when participants were asked to remain seated.

**Drug analysis**

Plasma concentrations of diltiazem and of two major metabolites, desmethyl-diltiazem (MA) and deacetyldiltiazem (DAD), were measured by HPLC. Essentially, the technique used is as follows: the parent compound and both metabolites are extracted from the plasma at a neutral pH=7.5 with methyl tert-butyl ether. The compounds are then back-extracted from the organic solvent with sulphuric acid 0.05 N. The extracted compounds were separated on an ODS 10 μm column with acetonitrile: phosphate buffer 0.005 M pH=3.0:dibutylamine (38:62:0.4 v/v/v) as the mobile phase and detected (at 229 nm) with a Spectroflow 757, Kratos UV detector. The sensitivity of the method is 2.5 ng ml⁻¹ of plasma, although concentrations as low as 1 ng ml⁻¹ can be detected. Recovery of D, MA, and DAD was, respectively, 93.0 per cent, 72.5 per cent, and 94.0 per cent and the coefficient of variation was lower than 10 per cent for the concentrations of the calibration curve.

**Pharmacokinetic analysis**

The following pharmacokinetic parameters were derived from diltiazem plasma concentrations: $C_{\text{max}}$, $t_{\text{max}}$, $k_d$, $k_m$, $k_{el}$, $t_{1/2}$, and AUC$_\infty$. The maximum
plasma concentration ($C_{max}$) and the time to reach maximum plasma concentration ($t_{max}$) were observed values. The absorption rate constant ($k_a$) or in the case of the metabolites the formation rate constant ($k_m$) and the apparent elimination rate constant ($k_e$) were determined by linear least squares regression analysis of the residual and terminal log-linear portion of the concentration versus time curve. As calculated, the $k_m$ values represent a slight underestimation of the real value. In most cases, diltiazem conferred to the body the characteristics of a two-compartment open model, as determined by the graphical representation of the decline of the plasma concentration–time curve. In some individuals, the absorption rate was slow enough to mask the distribution phase and under these circumstances, it was considered that diltiazem conferred to the body the characteristics of a one-compartment open model. Therefore, plasma concentrations of diltiazem, MA, and DAD were fitted to a one- or a two-compartment model using a nonlinear regression curve-fitting program (PC-NONLIN). The area under the plasma versus time curve (AUC) from 0 to 24 h was determined by the trapezoidal rule and the AUC from 24 h to infinity was estimated by dividing the concentration at 24 h by the elimination rate constant. Total AUC, from 0 to $\infty$ ($AUC_{\infty}$) was the sum of the estimated AUCs from 0 to 24 h and from 24 h to $\infty$. The intrinsic clearance of diltiazem was calculated by dividing the oral dose by $AUC_{\infty}$.

Statistical analysis

Comparisons to assess the effect of food on diltiazem pharmacokinetics were carried out using an analysis of variance for a $2 \times 2$ Latin square design study.
According to previous trials, this design with 24 subjects should yield a $p$ value of 0.2 if $\alpha$ is set at 0.05. Comparisons of the two formulations were carried out using a one-way analysis of variance. A maximum difference of 20 per cent ($\Delta = 20$ per cent) was accepted in mean value for the AUC$_{\infty}$.

RESULTS

Single dose of a conventional formulation of diltiazem

The mean plasma concentration profiles of a conventional formulation of diltiazem (60 mg) administered with or without food are depicted in Figure 1. As shown, food did not affect diltiazem plasma concentrations. The absorption rate of diltiazem under the two experimental conditions was assessed by $C_{\text{max}}$, $t_{\text{max}}$, and $k_a$, whereas the relative extent of absorption was estimated by the AUC$_{\infty}$ (Table 1). The presence of food did not modify either the rate or the extent of absorption of diltiazem. No statistical difference was detected with any of the absorption pharmacokinetic parameters under study. Assuming that absorption was complete, the estimated intrinsic clearance of the drug was 3961 ± 313 ml min$^{-1}$ in the absence of food, and was not influenced by food, e.g. 3585 ± 303 ml min$^{-1}$. The terminal half-life of diltiazem was not modified by the presence of food (Table 1); it was 4.3 ± 0.5 h under fasting conditions and 4.6 ± 0.4 h after the ingestion of food.

The rate of generation of desmethyldiltiazem (MA) and deacetyldiltiazem (DAD), the two major metabolites of diltiazem, could be assessed by estimating the $C_{\text{max}}$, $t_{\text{max}}$, $k_m$, and AUC$_{\text{M}}$ (Table 1). The two metabolites were generated at the same rate ($k_m$, $t_{\text{max}}$) although not to the same extent ($C_{\text{max}}$, AUC$_{\text{M}}$); $k_m$ and $t_{\text{max}}$ were approximately 0.9 h$^{-1}$ and 3.0 h for both metabolites, whereas $C_{\text{max}}$ and AUC$_{\text{M}}$ of MA were more than double compared to DAD. The presence of food did not modify either the speed or the extent of formation of the metabolites.

Single dose of a slow-release formulation of diltiazem

The mean plasma concentration profile of a slow-release formulation of diltiazem (120 mg) administered with or without food is depicted in Figure 2. As can be observed, food did not affect diltiazem plasma concentrations. The pharmacokinetic parameters used to measure the rate and extent of absorption and the elimination of the conventional formulation of diltiazem were also used for the slow-release formulation. $C_{\text{max}}$, $t_{\text{max}}$, $k_a$, AUC$_{\infty}$, and $t_{1/2}$ of diltiazem were estimated under fasting and non-fasting conditions (Table 2) and as with the conventional formulation, none of these parameters was affected by the presence of food.

The administration of a slow-release formulation of diltiazem under fasting conditions resulted in a $t_{\text{max}}$ significantly increased from 2.6 ± 0.2 to 7.1 ± 0.2 h ($p<0.001$) when compared to the conventional formulation. Interestingly, the AUC$_{\infty}$ corrected by the dose ratio (478 ± 43 ng.h ml$^{-1}$) for the slow-release
Table 1. Pharmacokinetic parameters of diltiazem and its two metabolites, desmethyldiltiazem (MA) and deacetyldiltiazem (DAD), following the single administration of 60 mg of diltiazem (2 × 30 mg conventional tablets) under fasting and non-fasting conditions*.  

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>MA</th>
<th>DAD</th>
<th>Diltiazem</th>
<th>Non-fasting</th>
<th>MA</th>
<th>DAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng ml$^{-1}$)</td>
<td>41.5 ± 2.7</td>
<td>13.1 ± 0.9</td>
<td>6.3 ± 0.5</td>
<td>48.1 ± 4.5</td>
<td>13.6 ± 1.1</td>
<td>7.2 ± 0.7</td>
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<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>2.6 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>2.8 ± 0.3</td>
<td>2.8 ± 0.2</td>
<td>3.5 ± 0.3</td>
<td>3.1 ± 0.2</td>
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<tr>
<td>$k_a$ (h$^{-1}$)</td>
<td>1.17 ± 0.16</td>
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<tr>
<td>$k_{\text{m}}$ (h$^{-1}$)</td>
<td>0.87 ± 0.11</td>
<td>0.94 ± 0.11</td>
<td></td>
<td>0.89 ± 0.12</td>
<td>0.84 ± 0.08</td>
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<tr>
<td>$AUC_{\text{tr}}$ (ng·h ml$^{-1}$)</td>
<td>283.1 ± 18.5</td>
<td>139.8 ± 12.2</td>
<td>50.4 ± 5.9</td>
<td>318.3 ± 24.4</td>
<td>148.7 ± 12.6</td>
<td>64.9 ± 9.3</td>
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<td>$t_{1/2}$ (h)</td>
<td>4.3 ± 0.5</td>
<td>6.0 ± 0.6</td>
<td>5.2 ± 0.8</td>
<td>4.6 ± 0.4</td>
<td>6.3 ± 0.6</td>
<td>8.3 ± 2.1</td>
<td></td>
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</tbody>
</table>

*Values represent mean ± SEM for 24 subjects.

Table 2. Pharmacokinetic parameters of diltiazem and its two metabolites, desmethyldiltiazem (MA) and deacetyldiltiazem (DAD), following the single administration of 120 mg of diltiazem (1 × 120 mg slow release capsule) under fasting and non-fasting conditions*.  

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>MA</th>
<th>DAD</th>
<th>Diltiazem</th>
<th>Non-fasting</th>
<th>MA</th>
<th>DAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng ml$^{-1}$)</td>
<td>99.0 ± 9.8</td>
<td>25.2 ± 1.2</td>
<td>8.9 ± 0.7</td>
<td>101.6 ± 7.1</td>
<td>30.4 ± 1.7</td>
<td>9.4 ± 0.6</td>
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<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>7.1 ± 0.2</td>
<td>8.6 ± 0.5</td>
<td>8.3 ± 0.4</td>
<td>7.1 ± 0.2</td>
<td>8.5 ± 0.3</td>
<td>8.8 ± 0.3</td>
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<tr>
<td>$k_a$ (h$^{-1}$)</td>
<td>0.35 ± 0.03</td>
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<tr>
<td>$k_{\text{m}}$ (h$^{-1}$)</td>
<td>0.27 ± 0.02</td>
<td>0.35 ± 0.04</td>
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<td>0.26 ± 0.02</td>
<td>0.25 ± 0.02</td>
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<tr>
<td>$AUC_{\text{tr}}$ (ng·h ml$^{-1}$)</td>
<td>955.0 ± 85.9</td>
<td>433.7 ± 27.3</td>
<td>177.2 ± 18.9</td>
<td>834.9 ± 55.3</td>
<td>428.4 ± 26.0</td>
<td>167.3 ± 14.5</td>
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<tr>
<td>$t_{1/2}$ (h)</td>
<td>5.1 ± 0.2</td>
<td>8.6 ± 0.3</td>
<td>12.9 ± 1.2</td>
<td>4.9 ± 0.2</td>
<td>8.0 ± 0.4</td>
<td>12.8 ± 1.4</td>
<td></td>
</tr>
</tbody>
</table>

*Values represent mean ± SEM for 24 subjects.
Figure 2. Mean plasma concentrations of diltiazem following the ingestion of 120 mg of a slow-release capsule of diltiazem in fasting (*) and non-fasting (▲) healthy volunteers. Vertical bars are SEM.

formulation was significantly higher ($p<0.01$) than the AUC$_w$ estimated after the administration of the conventional formulation (283 ± 19 ng.h ml$^{-1}$). The terminal half-life of diltiazem was not influenced by the formulation; it was 4.3 and 5.1 h for the conventional and slow-release formulation, respectively.

As could be expected, MA and DAD rate of formation was slower with the slow-release formulation of diltiazem (Table 2). The formation rate constant ($k_m$) was decreased to approximately 0.3 h$^{-1}$ with the slow-release compared to 0.9 h$^{-1}$ with the conventional formulation. The $t_{max}$ values for MA (8.6 vs 3.5 h) or DAD (8.3 vs 2.8 h) were always longer with the slow-release formulation. After correction for the dose ratio, the amounts of metabolites were higher ($p<0.01$) than predicted on the basis of the AUC$_w$ obtained with the administration of the two conventional tablets of 30 mg; the increase was 56 per cent for MA and 77 per cent for DAD. As with the conventional formulation of the drug, the presence of food did not modify either the rate or the extent of formation of metabolites.

**DISCUSSION**

The results observed in this study demonstrate that the sustained-release capsule considerably slowed the absorption of diltiazem, as reflected by the decrease in diltiazem absorption rate constant and the increase in $t_{max}$. In addition, this formulation decreased the maximal fluctuation in diltiazem plasma concentrations ($C_{max} - C_{12})/(AUC_{0-12})/\tau$) from 84 to 45 per cent where $\tau$ is the dosage
interval. It is noteworthy that the slow-release capsule formulation increased diltiazem bioavailability considerably (69 per cent, \(p<0.001\)), compared to the conventional tablet. Interestingly, this increase in bioavailability was not observed in the study of Gordin et al.\(^1\); this discrepancy could be explained by any of four mechanisms: the first may be related to differences in the slow-release formulation, since Gordin et al.\(^1\) showed lower values for \(C_{\text{max}}\) (54 ± 4 ng ml\(^{-1}\)) and \(t_{\text{max}}\) (2.7 ± 0.3 h) and they estimated a slightly higher fluctuation (54 per cent); the second factor refers to the dose used and possibly to a saturable first pass, since Gordin et al.\(^1\) used 120 mg for both formulations, whereas we compared 60 mg of diltiazem for the conventional tablet and 120 mg for the slow-release capsule; the third mechanism could be related to a decreased absorption of diltiazem when administered in the conventional 30 mg tablet; and, finally, the difference could be explained on the basis of a higher clearance in the group of subjects that received the 30 mg \((\times 2)\) tablets.

With the present data it is difficult to reach any final conclusion about the mechanisms involved in the increase in bioavailability observed after the administration of the slow-release formulation. However, the average \(\text{AUC}_{\infty}\) estimated following the administration of the 120 mg slow-release formulation is identical to the average values of \(\text{AUC}_{\infty}\) reported by Morselli et al.,\(^8\) following the administration of 120 mg in a gelatine capsule, or by Gordin et al.\(^1\) using a slow-release formulation; these data suggest that in the present study, the bioavailability of diltiazem administered as a slow-release capsule conforms to other standards and as a consequence, probably does not explain the relative increase in \(\text{AUC}_{\infty}\) compared to the 2 × 30 mg conventional tablets. On the other hand, in the present study, average \(\text{AUC}_{\infty}\) values for the 2 × 30 mg conventional tablets was similar to the values reported by Hermann et al.\(^5\)

Morselli et al.\(^8\) suggested that the bioavailability of diltiazem is dose dependent for doses ranging from 60 to 210 mg, since they observed peak plasma concentrations of 65 ± 9 and 315 ± 60 ng ml\(^{-1}\), respectively; on the other hand, another study\(^9\) reports that the bioavailability of diltiazem was not affected by doses ranging from 60 to 120 mg. In the present study, the ratio \(\text{AUC}_{\infty}\) 120 mg to \(\text{AUC}_{\infty}\) 60 mg of diltiazem and of the metabolites was increased by 69 per cent for diltiazem, by 56 per cent for MA and by 77 per cent for DAD, suggesting that the clearance of diltiazem was not dose-dependent, and was not increased in the group of volunteers receiving the 2 × 30 mg tablet, otherwise the estimated ratio for metabolites would have decreased. Therefore, assuming that the metabolites assayed reflect the extent of first pass, the relative increase in \(\text{AUC}_{\infty}\) observed after the administration of the slow-release capsules (compared to the 2 × 30 mg tablets) is probably not related to the slow-release formulation itself, but rather, secondary to the inter-individual variability or to a more complete absorption of diltiazem administered in a capsule. Further studies are required to elucidate these observations.

Food did not alter the bioavailability of the conventional tablets or of the slow-release capsules of diltiazem. This is interesting because food could have
influenced diltiazem bioavailability by two different mechanisms: firstly, by altering diltiazem presystemic clearance and, secondly, by modifying the rate of dissolution of the slow-release preparation. In the present study neither of these phenomena appears to be influenced by food. These results agree with reports showing that the bioavailability of two other calcium influx-blocking dihydropyridine derivatives, nifedipine\(^1\) and nicardipine,\(^1\) both highly extracted by the liver, when administered as conventional formulations, were not affected by food. However, our results contrast with the fact that the rate of absorption of nifedipine, when administered as a biphasic release preparation, was decreased by food,\(^1\) probably because food reduced the rate of dissolution of the biphasic tablet.

The amount of drug reaching the systemic circulation of selected compounds, subjected to presystemic clearance, such as propranolol, metoprolol, labetolol, and hydralazine,\(^2\) is increased when administered with food. On the other hand, the bioavailability of a number of drugs, also subjected to presystemic first pass, is not modified by the intake of food, for example, nifedipine,\(^1\) nicardipine,\(^1\) pindolol, amitriptyline, prazosin, zimelidine, dextropropoxyphene, codeine, and melperone.\(^2\) The present results indicate that diltiazem can be added to the latter list of drugs. The mechanisms underlying such differences are not clearly understood, but it does not appear that they are secondary to the content in carbohydrates or proteins of the meal given.\(^3\) It has been shown that the administration of a vasodilator (hydralazine), just before the intake of propranolol, increased its bioavailability\(^4\) in a comparable fashion to food. However, these differences cannot be explained solely by changes in intestinal blood flow,\(^5\) as it must be assumed that in all cases food elicited the same effect on the splanchnic blood flow. The increase in bioavailability must also be associated with the physicochemical characteristics of the molecule itself, to the site where the presystemic metabolism is taking place, intestine or liver, and to the intrinsic clearance.

Food does not affect the bioavailability of hydralazine\(^6\) and propranolol\(^7\) when administered as slow-release formulations, whereas food increases the bioavailability of the conventional formulations. In addition, the administration of hydralazine does not increase the bioavailability of propranolol administered as a slow-release formulation.\(^8\) This indicates that when these drugs are administered in slow-release formulations, the liberation of the drug is independent of changes carried out by food and in addition, compared to the conventional tablet, it shows that food-induced changes in bioavailability are time- or site-dependent. In the present study it has been shown that food does not affect the bioavailability of a slow-release formulation of diltiazem. It can therefore be concluded that the rate of dissolution of the slow-release formulation is not affected by the changes induced by food in the stomach and upper small intestine.

At present six metabolites of diltiazem have been identified and quantified in human biological fluids.\(^9\) As a first biotransformation step, diltiazem could
be either demethylated to generate N-monodemethyldiltiazem (MA) or deacetylated to desacetyldiltiazem (DAD). These two metabolites may undergo further biotransformation to O-demethyldesacetyldiltiazem (M₄), to N-demethyl-desacetyldiltiazem (M₂) or N,O-didemethyldesacetyldiltiazem (M₆). Despite the identification of these metabolites in humans, the kinetics of diltiazem are still poorly understood. Some authors reported that DAD was a major metabolite,²⁷,²⁸ while others have failed to detect any DAD in the plasma of patients treated with diltiazem. This raised some concerns as to whether DAD is a true metabolite or a degradation product. In this regard, the differences observed in the concentrations of DAD could very well be dependent on the various specimen collection and analytical procedures used.³¹ In the present study, plasma concentrations of MA were around one-half and DAD one-fifth of diltiazem plasma concentrations, independent of the dose administered; our results suggest that DAD probably represents a true metabolite.

The intensity of the effect of a drug administered orally is closely related to its rate of absorption and to the amount of drug reaching the systemic circulation, in the way that the higher are these two parameters the stronger will be the response to the drug, the reverse being also true. For drugs with a narrow therapeutic range, changes in bioavailability may, therefore, influence the therapeutic outcome. The fact that the bioavailability of diltiazem, administered as a conventional tablet or as a slow-release capsule is not affected by food is certainly of practical significance because it helps to predict plasma concentrations and response throughout the day, more accurately.

REFERENCES