Antihypertensive Effect of Amlodipine and Lack of Interference With Cyclosporine Metabolism in Renal Transplant Recipients

Olivier Toupane, Sylvie Lavaud, Eric Canivet, Corine Beruda, Jean-Michel Hotton, Jacques Chanard

Abstract  The catabolism of various calcium channel blockers through cytochrome P-450 is heterogeneous and may be modified by concomitant use of cyclosporin A. In an open study we investigated the antihypertensive effect and clinical tolerance of the dihydropyridine amlodipine and its effects on cyclosporine kinetics in stable hypertensive renal transplant recipients not taking corticosteroids. Ten adult hypertensive patients grafted for 21.4±8.9 months and well stabilized with normal renal function were included in the study. Renal artery stenosis was ruled out by normal Doppler echography. After 2 weeks of placebo, amlodipine was started at a daily dose of 5 mg. The dose was then adjusted to 10 mg if necessary. Blood and urine chemistries and whole-blood cyclosporine trough levels were measured weekly. Cyclosporine kinetics were determined on a hourly basis before amlodipine administration and after 4 weeks of treatment. Normal blood pressure was obtained with the use of 5 mg/d amlodipine in 7 patients and 10 mg/d in 3, diastolic blood pressure decreasing from 98.7±3.8 to 81.3±9.1 mm Hg (P=.0007). Heart rate slightly increased by 10% (P<.02). The drug was well tolerated, and only minor ankle edema was found in 3 patients. Cyclosporine doses were not modified and cyclosporine levels remained unchanged throughout the study. Cyclosporine kinetic parameters were not significantly different at the beginning and end of the study. Bioequivalence was demonstrated indicating that cyclosporine biotransformation was not altered by the concomitant administration of amlodipine. We conclude that amlodipine at the dosage of 5 to 10 mg/d is an efficient calcium channel blocker in hypertensive renal transplant recipients treated with cyclosporine without corticosteroids. Moreover, amlodipine does not interfere with cyclosporine diffusion and metabolism. (Hypertension. 1994:24:297-300.)

Key Words • calcium channel blockers • antihypertensive agents • transplantation • cyclosporine • amlodipine • pharmacokinetics

In the transplanted patient treated with cyclosporine, all drugs that may modulate cytochrome P-450 activities can induce deleterious effects. Interference with cyclosporine metabolism induces either an increase of blood cyclosporine levels, and consequently potentiation of cyclosporine nephrotoxicity, or a decrease of cyclosporine levels, with a risk of acute rejection. Among the various drugs that interfere with cyclosporine metabolism are some members of the calcium channel blocker family, which are particularly efficient in treating the hypertension that occurs in more than 80% of transplant recipients. Diltiazem, verapamil, and nicardipine increase cyclosporine levels by competitive inhibition of cytochrome P-450 activities, whereas other calcium channel blockers, such as nifedipine, nitrendipine, and isradipine, do not interact with cyclosporine significantly.

We undertook the present study in the hypertensive renal transplanted patient on cyclosporine without corticosteroids to test the effects of the long-acting dihydropyridine amlodipine. Our goals were (1) to test the antihypertensive effect and tolerance of the drug given as unique antihypertensive therapy and (2) to detect any change in cyclosporine kinetics in the particular setting of coadministration with amlodipine.

Methods  Ten hypertensive renal transplant recipients entered the open clinical phase II study, the objectives of which were to define (1) the antihypertensive effects and tolerance of the calcium channel blocker amlodipine in patients on an immunosuppressive regimen consisting of cyclosporine without corticosteroids and (2) the effects of amlodipine administration on cyclosporine pharmacokinetics. Four patients were men and six women. Their mean age was 44.3±9.5 years (25 to 58) and their mean weight 68.5±17 kg (43.5 to 101.2). They had received a cadaver kidney 21.4±8.9 months before the study and were stable on an immunosuppressive therapy that consisted of cyclosporine monotherapy in seven patients and cyclosporine in association with azathioprine in three. Hypertension was treated with drugs, and renal artery stenosis was ruled out on the basis of a normal Doppler echography investigation. All the patients gave informed consent, and the study was conducted according to legal regulations after approval by the Ethics Committee of our institution.

Protocol  Amlodipine was given after a run-in period of 2 weeks of placebo administration. The enrolled patients continued their immunosuppressive regimen throughout the study. Patients were included in the protocol if diastolic blood pressure had
become higher than 95 to 115 mm Hg at the end of the placebo period. Amlodipine was started at the dosage of 5 mg/d. After 2 weeks the dose was increased to 10 mg if diastolic blood pressure was not normalized. Blood chemistry and renal function were checked weekly as well as cyclosporine whole-blood trough levels. Cyclosporine doses were adjusted if necessary to maintain the whole-blood trough level in the range of 70 to 200 µg/L. Pharmacokinetics of cyclosporine were determined on an hourly basis before and 4 weeks after amlodipine therapy. Blood samples were drawn after the morning dose of cyclosporine or that of either placebo or amlodipine. The final evaluation was made after 4 weeks of therapy.

**Statistics**

Results are given as mean±SD for quantitative values. ANOVA was used to compare blood pressure values, cardiac heart rate, and blood chemistry. Among the cyclosporine kinetic parameters, the area under the curve (AUC) was calculated according to the trapeze method. Maximal blood concentration (Cmax) and AUC, 90% confidence intervals were expressed as natural values (percentage of the means before treatment) and logarithms (ratio of the means after and before treatment) to define the biotransformation equivalence of cyclosporine given either alone or in association with amlodipine. Estimation of bioequivalence was calculated according to the 90% confidence interval method and the method of Schuirmann based on two one-sided tests.

**Results**

**Blood Pressure**

Two weeks after placebo had been administered, systolic blood pressure was 160.9±10.23 mm Hg and diastolic blood pressure 98.70±3.80. After 28 days of treatment, amlodipine significantly decreased blood pressure to 137.10±10.44 and 81.25±9.07 mmHg for systolic and diastolic levels, respectively (P<.001), as shown in Fig 1. Seven patients had diastolic blood pressure below 95 mm Hg after 2 weeks of therapy at 5 mg/d. Increasing the dose to 10 mg in the three remaining patients was required to achieve this end point. Heart rate increased slightly but significantly from 70 to 80 beats per minute (P=.0195).

**Clinical Tolerance**

Ankle edema was found in three patients and was the only side effect that occurred. The calcium channel blocker was otherwise well tolerated.

**Clinical Chemistry**

Renal function remained unchanged; serum creatinine was 130±32 and 122±33 µmol/L (P=NS), creatinine clearance 56±19 and 58±22 mL/min (P=NS), and urine proteins 0.20±0.30 and 0.25±0.33 g/d (P=NS) before and after amlodipine, respectively. Significant decreases were documented in the serum levels of uric acid, potassium, and phosphorus (Table 1). These changes are compatible with a tubular effect induced by amlodipine or by the coadministration of amlodipine and cyclosporine.

**Blood Concentration of Cyclosporine**

Cyclosporine daily doses were maintained constant at 253±87 and 252±87 mg/d before and after 28 days of amlodipine administration, respectively. Cyclosporine total blood trough levels remained unchanged throughout the study (112.9±24.1, 118±34.6, 107.9±33.8, 109.3±31.5, and 103.3±29.6 µg/L before and at weeks 1 through 4, respectively).

Table 2 summarizes the values of kinetic parameters of cyclosporine calculated at time 0, before amlodipine administration, and at day 28, at the end of the study. Pharmacokinetic parameters were derived from the curves shown in Fig 2. ANOVA did not show any significant difference between the values, indicating that amlodipine had not interfered with cyclosporine metabolism. This result, namely, the bioequivalence between the two study periods, was further confirmed by appropriate statistical tests, as recommended by Steinijans et al. The selected parameters for calculation were AUC, Cmax, and Cmax/AUC. Fig 3 clearly demonstrates that the 90% confidence intervals are within the limits of the accepted intervals of bioequivalence.

**Discussion**

Amlodipine is an efficient and safe drug with which to treat hypertension in the renal transplant recipient. At

**Table 1. Changes in Blood Chemistry After 4 Weeks of Amlodipine**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 0</th>
<th>Day 28</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, µmol/L</td>
<td>129.2±32.0</td>
<td>121.8±33.3</td>
<td>.2120</td>
</tr>
<tr>
<td>Uric acid, µmol/L</td>
<td>478.3±114.4</td>
<td>424.6±83.6</td>
<td>.0011*</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140.2±2.5</td>
<td>139.7±1.7</td>
<td>.5941</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.3±0.3</td>
<td>4.1±0.3</td>
<td>.0282*</td>
</tr>
<tr>
<td>Chloride, mmol/L</td>
<td>109.2±3.8</td>
<td>110.1±4.0</td>
<td>.5460</td>
</tr>
<tr>
<td>Total bicarbonates, mmol/L</td>
<td>26.0±3.6</td>
<td>26.0±4.3</td>
<td>.3389</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.37±0.17</td>
<td>2.29±0.13</td>
<td>.0516</td>
</tr>
<tr>
<td>Phosphorus, mmol/L</td>
<td>1.15±0.27</td>
<td>1.0±0.28</td>
<td>.0187*</td>
</tr>
</tbody>
</table>

*Significant change.

**Table 2. Pharmacokinetic Parameters of Cyclosporine Measured When Coadministered With Placebo (Day 0) or Amlodipine (Day 28)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 0</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, µg/L</td>
<td>564.3±150.9</td>
<td>592.4±162.4</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>2.40±1.51</td>
<td>2.60±1.96</td>
</tr>
<tr>
<td>AUC, µg·L⁻¹·h</td>
<td>1985±449</td>
<td>2059±474</td>
</tr>
<tr>
<td>Cmax/AUC, h⁻¹</td>
<td>0.29±0.036</td>
<td>0.29±0.071</td>
</tr>
</tbody>
</table>

Cmax indicates maximal blood concentration; Tmax, maximal time; and AUC, area under the curve. Values are mean±SD.
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Amlodipine in Renal Transplantation

Fig 2. Line graph shows kinetics of cyclosporine measured in total blood after the morning dose of cyclosporine plus placebo (initial testing) and that of cyclosporine plus amlodipine (final testing). Mean values are indicated.

The daily dose of 5 mg, 7 of 10 patients became normotensive within 2 weeks. In the 3 remaining patients, doubling the dose resulted in blood pressure normalization. With both doses, a slight but significant increase of pulse rate was observed.

Cyclosporine is the major immunosuppressive agent currently used in organ transplantation. Unfortunately, the drug is associated with hypertension and potential nephrotoxicity. Cyclosporine may cause direct vasoconstriction, increased response to circulating vasoactive hormones, and imbalance in the local production of vasoactive factors. Endothelin secretion is directly stimulated by cyclosporine. The vasodilating properties of calcium channel blockers appear particularly adequate to counteract the vascular effect of cyclosporine. Few long-term studies have been devoted to documenting the usefulness of cyclosporine monotherapy for the prevention of chronic rejection. Such a protocol seems valuable in some patients and represents a unique model for studying cyclosporine-drug metabolic interaction. It is the policy of our center to try immunosuppressive monotherapy after 6 months of renal cadaver transplantation in order to avoid long-term administration of corticosteroids. Patient selection for maintenance monotherapy is based on medical history, previous HLA immunization, occurrence of early rejection episodes, and drug tolerance. At the time of amlodipine testing, 7 of 10 patients were on cyclosporine monotherapy and 3 on cyclosporine and azathioprine. Corticosteroids are known to interfere with cytochrome P-450, whereas azathioprine does not.

Some calcium channel blockers potentiate cyclosporine nephrotoxicity, a phenomenon reflected by the increase in serum creatinine. During the present study, serum creatinine, blood urea, and proteinuria remained unchanged. However, the serum levels of uric acid, phosphorus, and potassium significantly decreased, suggesting a possible proximal tubular defect, because glomerular filtration rate remained constant as well as serum sodium levels. Cyclosporine by itself has been reported to favor acute arthritis in relation to an increase in serum uric acid, whereas uric acid turnover rate was not modified. Consequently, the serum uric acid decrease is likely caused by amlodipine.

Fig 3. Graph shows bioequivalence of cyclosporine biodisponibility calculated during the placebo period (P) and after 4 weeks of amlodipine (A). Ninety percent confidence intervals of the area under the curve (AUC), maximal blood concentration (Cmax), and Cmax/AUC are enclosed within accepted limits, indicating the absence of significant changes induced by the calcium channel blocker.

\[
P = A
\]

\[
\begin{align*}
P & = A \\
\text{AUC} & = \text{P} \\
\text{Cmax} & = \text{P} \\
\text{Cmax/AUC} & = \text{P}
\end{align*}
\]

\[
\begin{array}{c}
\text{P/A} \\
\text{INTERVAL OF BIOEQUIVALENCE ACCEPTABILITY} \\
\text{90% CONFIDENCE INTERVAL}
\end{array}
\]
itself. This particular effect may be associated with the natriuretic and kaliopenic effect of the drug documented by Reams et al.\textsuperscript{27} The tubular mechanism by which it occurs requires additional studies.

Cyclosporine kinetics were evaluated before and 4 weeks after amlodipine administration. During the study, cyclosporine trough blood levels remained constant, and cyclosporine doses were unchanged. The curves depicting blood cyclosporine concentration versus time were similar, and derived parameters remained in the same range. With the use of bioequivalence comparison, similar biotransformation was demonstrated for cyclosporine for whether given alone or in association with amlodipine, all the calculated pharmacokinetic parameters being included in their respective intervals of acceptability. Note that none of the patients included in the present study had a cyclosporine kinetic pattern that differed apparently from the mean. This may indicate a certain degree of homogeneity that accounts for similar metabolic responses.

These results demonstrate that cyclosporine metabolism by cytochrome P-450–dependent monooxygenase systems in the liver and small bowel is not disturbed by amlodipine, suggesting an absent or nonsignificant competitive inhibition between the two drugs, as previously documented for other calcium channel blockers.\textsuperscript{3,5} Among more than 10 different forms of cytochrome P-450 that have been isolated and characterized in terms of molecular, spectral, enzymatic, and immunological properties, cytochrome P-450 III A4 seems the target of calcium channel blockers. However, the precise moiety of the drugs that regulate enzyme activity is not well elucidated, and so far, the molecular basis of why dihydropyridine calcium antagonists do not interfere with cyclosporine metabolism whereas verapamil does is unknown.\textsuperscript{1,3,8}

We did not observe any effect of amlodipine on the incidence of rejection episodes in treated patients. Whether amlodipine might interfere with the immunological status of the patient remains questionable. It has been suggested that some calcium channel blockers may improve graft survival\textsuperscript{25–26} by interfering with T cell activation.\textsuperscript{31} The clinical relevance of this effect is debated and was not investigated in the present study.

To conclude, the calcium channel blocking agent amlodipine does not interfere with cyclosporine kinetics in hypertensive transplant recipients. Its antihypertensive effect is significant after 2 weeks of administration and fully expressed after 4 weeks. The drug is well tolerated and can be prescribed in transplant recipients as it is prescribed in hypertensive nontransplanted patients.

References
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