Renal effects of amlodipine in normotensive renal transplant recipients

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Abstract Renal effects of amlodipine in normotensive kidney transplant recipients. The use of cyclosporin A (CsA) has improved the success of renal transplantation, but is associated with hypertension and significant renal toxicity. Previous reports suggest that calcium channel blockers may be useful in opposing the adverse effects of CsA. We have evaluated the effects of amlodipine (5 mg, once daily for 8 weeks) on renal function in 27 normotensive renal transplant recipients with stable renal function, in a double-blind, placebo-controlled, multicentre, cross over study. Amlodipine significantly reduced serum creatinine concentration relative to placebo (mean ± SD: 168 ± 65 vs 177 ± 66 μmol/l; P = 0.002) and there was a strong trend towards an increase in effective renal plasma flow on amlodipine relative to placebo (238 ± 92 vs 217 ± 87 ml/min; P = 0.055). Glomerular filtration rate and lithium clearance were unaffected. Trough CsA blood concentration was unaffected. Amlodipine was well tolerated, with a low incidence of adverse events, and did not affect blood pressure or heart rate. In conclusion, amlodipine reduced serum creatinine in normotensive renal transplant recipients after only 8 weeks treatment, and was well tolerated in concomitant administration with CsA.

Key words: amlodipine; cyclosporin A; normotensive; serum creatinine

Introduction

Immunosuppressive therapy with cyclosporin A (CsA) greatly enhances long term survival of allografts in renal transplant patients [1]. The use of CsA following transplantation is also associated with vasoconstriction, particularly in the renal vasculature [2]. As a result, between 20 and 95% of patients develop hypertension, with a high proportion of patients also developing some degree of renal impairment. In 5–15% of patients, this does not resolve following withdrawal of CsA [3]. It has been suggested that the vasodilator action of calcium channel blockers may be useful in opposing the vasoconstrictor effects of CsA in renal transplant patients [4,5], and these agents have been reported to protect renal function in both the short and the long term [6]. Recent studies have indicated that the long-acting calcium channel blocker amlodipine improves allograft function in renal transplant patients more effectively than placebo, or angiotensin converting enzyme (ACE) inhibitors, which have been evaluated as another potentially useful vasodilator therapy in these patients [7,8]. Some calcium channel blockers, including the dihydropyridine nicardipine, may increase blood CsA concentrations through competitive inhibition of CsA metabolism at the level of cytochrome P-450 [9–13], thereby increasing the risk of renal toxicity. Thus, the actions of calcium channel blockers in patients with renal impairment are heterogeneous, complex, and require further investigation. The aim of the present study was to study the effects of amlodipine on graft function in CsA treated normotensive renal transplant recipients with renal insufficiency.

Methods

Study design

This was a multicentre, double-blind, two-way, cross over study to investigate the effects of amlodipine on renal function in normotensive, post-renal transplant patients with mild renal insufficiency during CsA treatment. Following a 12-week placebo run-in, patients were randomized into two treatment groups. The first active treatment period involved administration of either amlodipine or placebo; patients were then crossed over on to the alternative treatment for a further 8 weeks with no intervening washout period.

Patients

Patients included in the study were outpatients of either sex, 18–70 years of age, who had undergone renal allograft
Amlodipine and renal allograft function 385
transplant at least 3 months previously. Patients were normo-
tensive, defined as supine diastolic blood pressure (DBP) 
between 75 and 95 mmHg. Although renal function was 
impaired (serum creatinine between 2 and 7 μmol/l/kg body 
weight), this was stable for at least 12 weeks prior to 
randomization and patients were on a stable dose of CsA 
for at least 2 months prior to enrolment into the study. All 
patients gave informed consent.

Criteria for exclusion from the study included: patients 
who had received any drug within the previous 3 months 
which may have interfered with study medication; clinically 
significant concomitant disease; significant haematological or 
biochemical findings (apart from those associated with renal 
insufficiency); acute rejection of renal allograft within the 
last 3 months.

Treatments
Throughout the 12-week run-in period and during the treat-
ment phase of the study, patients were given encapsulated 
CsA (Sandimmun®) to ensure standardization of dosing. In 
addition to CsA, patients received other immunosuppressive 
medication (azathioprine and prednisolone), which they were 
asked to take at regular times and at constant dosage 
throughout the study. During each 8-week active treatment 
phase, amlodipine (5 mg) or matching placebo were adminis-
tered orally once daily.

Assessments
Serum concentrations of creatinine, urea and electrolytes 
were measured in venous blood samples at each visit during 
during the 12-week run-in and at the end of each treatment period. 
Lithium clearance, glomerular filtration rate (GFR; by 
plasma clearance of Tc-99m labelled DTPA), and effective 
renal plasma flow (ERPF; by plasma clearance of 125I-
labelled hippuran) were measured at the end of the run-in 
period and following each treatment period. Whole blood 
trough CsA concentrations were measured (using a radioimmunoassay method) on samples taken imme-
diately before oral administration of CsA.

Adverse events noted during treatment were recorded and 
designated as ‘drug related’, ‘possibly drug related’, or ‘not 
drug related’. The onset date, duration and severity (mild, 
moderate, or severe), and outcome were noted. The physician 
made an overall assessment of adverse effects at the end of 
each treatment period. A range of standard haematological 
and biochemical measurements were carried out at baseline 
and following each treatment period. Body weight and vital 
signs (heart rate and blood pressure, using an automated 
sphygmomanometer) were measured at each study visit, with 
vital signs also monitored 6 h after the CsA dose at baseline 
and after each treatment period.

Statistics
An estimated sample size of 24 patients was required to 
detect a difference in creatinine concentration of 30 μmol/l 
between treatments, with a power of 80% and a significance 
level of P = 0.05 (two-tailed), assuming a within patient 
standard deviation of treatment difference of 50 μmol/l. Data 
from all patients with measurements in both the placebo and 
amlodipine treatment periods were included in analysis. No 
period effects were found in the data, therefore data from 
both treatment sequences were analysed as a whole. 
Differences in means between treatments were explored using 
a parametric analysis of variance appropriate to a two-
treatment cross over trial [14].

Results

Demographics
Patients were allocated in equal numbers to receive either 
amlodipine or placebo as the first treatment (Table 1). The 
characteristics of patients in each treatment group were 
generally well matched. The ratio of males to females and 
body weight were very similar in each group, though the 
group which received placebo before amlodipine was slightly 
younger, and tended to have a longer duration of renal 
insufficiency, a longer time since transplant, lower serum 
creatinine, and a lower daily CsA dose. Of the 30 patients 
originally allocated to treatment groups, three patients did 
not receive both treatments and were not included in the 
final analysis. The safety analysis included 29 patients who 
received placebo and 28 patients who received amlodipine.

A total of 19 patients had concomitant conditions at 
screening, the most common of which were essential hyper-

tension in four patients (though these patients fulfilled the 
entry criterion of DBP < 95 mmHg), duodenal ulcers in 
three patients and oedema in three patients. Concomitant 
medications were recorded in 27 patients at screening, the 
most common of which were frusemide (nine patients), 
nifedipine (eight patients), and ranitidine (eight patients). 
One patient continued to receive nifedipine. All patients were 
receiving CsA at screening, and in some cases were also 
taking azathioprine (12 patients) and prednisolone (16 
patients). The distributions of concomitant conditions and 
therapies were similar for the two-treatment groups.

Effects on renal function and CsA concentrations
The effects of amlodipine on renal function are shown in 
Table 2. Serum creatinine remained similar to baseline during 
placebo administration, whereas this parameter was reduced 
significantly during amlodipine treatment. In addition, there 
was a strong trend for ERPF to increase during amlodipine 
treatment and to decrease during placebo treatment. The 
difference between the treatments almost achieved statistical 
significance (P = 0.055). Lithium clearance and GFR were 
not significantly affected by amlodipine, compared to 
placebo.

Trough CsA concentration, defined as the concentration 
right after the next dose, was unaffected by amlodipine 
(Table 2).

Tolerability
Adverse events, considered to be possibly related to treat-
ment, were reported by four patients receiving placebo, and 
consisted of ‘mild’ epistaxis, postural dizziness, leg cramps, 
and ‘moderate’ worsening of gout. Two patients receiving 
amlodipine reported treatment-related adverse events, 

described as ‘mild’ worsening of oedema together with 
‘severe’ epistaxis in one patient, and ‘moderate’ leg oedema, 
leading to withdrawal of treatment, in the other. There were 
no major shifts in laboratory or haematological variables 
during placebo or amlodipine. In the overall evaluation of 
tolerability, amlodipine was considered to be well tolerated 
with a low incidence of adverse effects.
Table 1. Demographics: all patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo→amlodipine</th>
<th>Amlodipine→placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Males : females</td>
<td>10:5</td>
<td>11:4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.5</td>
<td>45.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>Time since transplant (months)</td>
<td>51.4</td>
<td>39.0</td>
</tr>
<tr>
<td>Duration of renal insufficiency (years)</td>
<td>8.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>157</td>
<td>194</td>
</tr>
<tr>
<td>Daily dose of cyclosporin (mg)</td>
<td>307</td>
<td>347</td>
</tr>
</tbody>
</table>

Figures are means, where applicable, from 30 patients. Column headings refer to the order of treatments in the cross over design.

Table 2. Mean changes in renal function from baseline: intention-to-treat patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Placebo</th>
<th>Amlodipine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>176±51</td>
<td>177±66</td>
<td>168±65</td>
<td>0.002</td>
</tr>
<tr>
<td>Lithium clearance (ml/min)</td>
<td>11.8±6.3</td>
<td>11.4±9.5</td>
<td>10.3±7.2</td>
<td>0.504</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>45±15</td>
<td>47±15</td>
<td>49±20</td>
<td>0.334</td>
</tr>
<tr>
<td>Effective renal plasma flow (ml/min)</td>
<td>229±90</td>
<td>217±87</td>
<td>238±92</td>
<td>0.055</td>
</tr>
<tr>
<td>Trough blood cyclosporin concentration (ng/ml)</td>
<td>154±66</td>
<td>159±65</td>
<td>180±92</td>
<td>0.121</td>
</tr>
</tbody>
</table>

Figures are means ± SD of data from 23–27 patients. Significance values refer to differences between treatments.

**Haemodynamics**

The effects of amlodipine on BP and heart rate are shown in Table 3. Mean SBP fell slightly during treatment with placebo and amlodipine, by 6 and 8 mmHg, respectively. DBP was essentially unchanged on placebo and fell by an average of 4 mmHg on amlodipine. These changes were not statistically significant between treatments. Heart rate was unaffected by amlodipine.

**Discussion**

The purpose of this double-blind, placebo-controlled, cross over study was to evaluate the effects of amlodipine in renal transplant patients with impaired renal function, but without hypertension. Amlodipine was well tolerated, with a low incidence of adverse effects. The significant reduction in serum creatinine (P = 0.002) and the tendency towards an increase in ERPF (P = 0.055) indicated an improvement in renal function during amlodipine treatment. Such an improvement in serum creatinine, after only 8 weeks treatment of patients with stable renal impairment, contrasts with other studies, which have failed to demonstrate a significant effect of other calcium channel blockers on this parameter in renal transplant patients following treatment for up to 1 year [15–17]. The improvement in creatinine was not associated with a rise in GFR; this could be due either to a type II error (related to small numbers) or alternatively, to a pharmacological reduction in tubular reabsorption of creatinine or an increase in tubular secretion of creatinine (by amlodipine). However, this was not evaluated during this study and warrants further investigation.

However, several studies have demonstrated improvements in other indices of renal function in CsA treated transplant patients following treatment with amlodipine and other calcium channel blockers [4,7,8,17–20]. The degree of renal protection afforded by amlodipine compares favourably with that of ACE inhibitors. In one study, 8 weeks of treatment with amlodipine was more effective than ACE inhibition with perindopril in increasing lithium and urate clearance [8]. A further study showed that 4 weeks treatment with amlodipine, but not with the ACE inhibitor lisinopril, increased GFR and ERPF, and reduced renal vascular resistance [7].

In assessing the renal protective effects of calcium channel blockers, it is difficult to separate direct effects on the kidney from benefits resulting from indirect

Table 3. Mean changes in blood pressure and heart rate: intention-to-treat-patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Placebo</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>72±13</td>
<td>72±12</td>
<td>71±11</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>147±18</td>
<td>141±19</td>
<td>139±18</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85±6</td>
<td>84±10</td>
<td>81±12</td>
</tr>
</tbody>
</table>

Figures are means ± SD from 27 patients. There were no significant differences between treatments.
Amlodipine and renal allograft function

References


haemodynamic effects [21]. Most previous reports of the renal effects of amlodipine are from studies in hypertensive renal transplant patients [5,7,8] or hypertensive patients with diabetic nephropathy [22]. The effects of vasodilator treatments on renal function in these patients do not consistently parallel their haemodynamic effects, suggesting that other protective mechanisms may be involved. For example, the reduction in proteinuria by amlodipine in diabetic nephropathy is comparable to that of ACE inhibitors, but is superior to that of nifedipine, despite the potent antihypertensive effects of all three therapies in these patients [23–28]. Furthermore, the beneficial renal effects of amlodipine observed in the present study occurred in the absence of marked changes in BP or renal haemodynamics. Thus, a direct protective effect of amlodipine on the kidney is likely.

Further studies of the effects of amlodipine in normotensive patients with renal insufficiency would resolve this question. However, the definition of ‘normotensive’ may vary between subgroups of patient groups within such a study, particularly with regard to diabetics. Patients in the present study were considered functionally normotensive by our criteria (DBP < 95 mmHg), although some had been taking antihypertensive medication before the study. These criteria comply with guidelines recommending that pharmacological intervention is not required in patients whose diastolic blood pressure is in the lower end of the range 90–99 mmHg [29]. However, recent guidelines for BP control, particularly in the US [30], have set limits for BP at levels as low as 130/85 mmHg for normal blood pressure, with pressures of 130–139/85–89 mmHg considered to be high-normal. The mean baseline values of DBP and SBP in our patients (85 ± 6 and 147 ± 18 mmHg) suggest that some of our patients could conceivably be classified as borderline hypertensive under such strict guidelines. This issue would need to be addressed in the design of future studies in ‘normotensive’ patients.

Although some studies have demonstrated statistically, but not clinically, significant increases in CsA concentrations during amlodipine treatment of patients who were concomitantly treated with steroids [7,8], in this study the trough concentration of CsA was unaffected by amlodipine. The bioavailability of the CsA preparation used in this study is known to be highly variable, being between 1 and 98% [1]. Consequently, the ability of studies using oral administration to demonstrate interactions between CsA and other agents is extremely limited. Pharmacokinetic studies specifically designed to investigate possible interactions would therefore be of value. However, there is at present insufficient evidence from this and other studies, in which drugs were given by the oral route, to support an interaction between amlodipine and CsA.

In conclusion, the administration of amlodipine following renal transplantation, produced a fall in serum creatinine in normotensive patients with stable renal insufficiency treated with CsA, after only 8 weeks of treatment. Amlodipine was well tolerated in these normotensive patients, and has well documented efficacy in hypertension. The long duration of action of amlodipine, with relatively stable blood levels over time, contributes to its suitability for concomitant administration with CsA.


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