Abstract

Background. Hypertension and hyperuricaemia are common side-effects of cyclosporin A (CsA) treatment in renal transplant recipients. While it is well established that the calcium channel blocker amlodipine can control CsA-induced hypertension effectively in this patient population, recent evidence suggests amlodipine might also reduce hyperuricaemia. The present study was designed to compare the effects of the calcium channel blocker amlodipine (5–10 mg/day) and the β-adrenoceptor antagonist tertatolol (5–10 mg/day) on CsA-induced hyperuricaemia in post-renal transplant recipients with hypertension.

Methods. Forty-eight hypertensive renal transplant recipients on a stable dose of CsA were randomized in a double-blind, parallel-group manner to receive either amlodipine (n = 24) or tertatolol (n = 24) for 60 days. The primary outcome measure was the change from baseline in serum uric acid concentration. Secondary analyses of efficacy were based on changes in renal function and blood pressure.

Results. Amlodipine significantly decreased serum uric acid levels from 483 ± 99 to 431 ± 110 μmol/l (P < 0.001), while tertatolol significantly increased uric acid from 450 ± 98 to 476 ± 84 μmol/l (P = 0.006). Amlodipine also significantly increased glomerular filtration rate (P = 0.0048) and the clearance rate of uric acid (P = 0.023) and it reduced the fractional proximal tubular reabsorption of sodium (P < 0.001), compared with tertatolol. Renal plasma flow and filtered fraction were unaffected by both treatments, as was trough CsA blood concentration. Amlodipine lowered systolic blood pressure to a significantly greater extent than did tertatolol (P = 0.007). The time-dependent profile of diastolic blood pressure did not differ significantly between treatment groups. Both drugs were well tolerated.

Conclusions. Amlodipine could be more appropriate than tertatolol for CsA-induced hypertension and hyperuricaemia in renal transplant recipients.

Keywords: amlodipine; calcium channel blockade; cyclosporin A; gout; hyperuricaemia; renal transplantation

Introduction

The use of cyclosporin A (CsA) as an immunosuppressive agent following renal transplantation has reduced the incidence of acute rejection and increased long-term survival [1]. Unfortunately, CsA can also cause vasoconstriction, especially in the renal vasculature. A single dose of CsA (3.5 mg/kg) administered to renal transplant recipients has been shown to reduce the glomerular filtration rate (GFR) by ~50% within 6 h [2]. As a result, long-term treatment with CsA commonly results in several potentially serious side-effects, including systemic hypertension, permanent renal damage, cardiovascular disease and numerous metabolic abnormalities [3].

One frequent metabolic consequence of CsA-induced vasoconstriction is a decreased capacity to excrete uric acid [3,4]. Approximately 80% of patients administered CsA exhibit high serum levels of uric acid (hyperuricaemia) [5,6]. The precipitation and deposition of excess uric acid within the articular cartilage of joints can ultimately present as arthritic gout. Indeed, gout constitutes a cause of considerable morbidity among renal transplant recipients who are administered CsA, afflicting as many as 10% of patients 2 years after transplantation [6].

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Calcium channel blockers (CCBs), such as the dihydropyridines, are a mainstay of antihypertensive treatment in the renal transplant patient, chiefly because of their preferably pre-glomerular vasodilating properties [7]. For example, it has been well established that the dihydropyridine CCB, amlodipine, can control blood pressure in hypertensive renal transplant recipients without deleteriously modifying the immunosuppressive effects of CsA [8,9]. In addition, a recent study also identified that amlodipine significantly reduced hyperuricaemia in recipients of CsA-treated renal allografts, compared with the angiotensin-converting enzyme (ACE) inhibitor, perindopril [10]. The aim of the present study was to compare the effects of amlodipine and a non-selective β-adrenoceptor, tertatolol, on the urinary elimination of uric acid in CsA-treated renal transplant recipients with hypertension.

Subjects and methods

Patient selection

Male and female patients were recruited at three centres in France and had undergone renal transplantation at least 6 months previously. Patients were ≥18 years of age, hypertensive [diastolic blood pressure (DBP) between 90 and 100 mmHg and/or systolic blood pressure (SBP) between 140 and 180 mmHg] and on a stable dose of CsA (plasma concentration 70–200 μg/l) for at least 3 months.

Criteria for exclusion from the study included severe renal (creatinine clearance <10 ml/min), cardiac and/or hepatic insufficiency; any clinically significant concomitant disease (cerebrovascular accident, unstable angina, myocardial infarction, diabetes, asthma, Raynaud’s syndrome and bradycardia) and concomitant treatments, including CCBs, other than those required for the study, non-steroid anti-inflammatory drugs, antidepressants, quinidinones, amiodarone, neuroleptics, aminosides, cephalosporins, diuretics, thiazides and hypoglycaemic agents.

The study protocol was approved by an independent ethics committee (CCPPRB Reims) and was conducted in accordance with the ethical principles of the Declaration of Helsinki and with European Guidelines for Good Clinical Practice. All patients gave informed consent.

Study design

This was a 75 day, comparative, randomized, parallel-group, double-blind study, consisting of a run-in period (days –15 to 0) and a treatment phase (days 0–60). All participants were administered placebo during the run-in period and, at day 0, were randomized to receive either amlodipine 5 mg/day or tertatolol 5 mg/day. This dose was maintained throughout the study if, by day 30, DBP had fallen below 90 mmHg and/or SBP below 140 mmHg. If blood pressure remained high (DBP between 90 and 110 mmHg and/or SBP between 140 and 180 mmHg), however, the dose of both drugs was doubled to 10 mg/day. Amlodipine and tertatolol capsules were taken orally and were indistinguishable from one another. Clinical evaluations were performed on days 0, 15, 30 and 60.

Outcome measures

The primary outcome measure, with respect to comparing the efficacy of amlodipine and tertatolol on CsA-induced uricaemia, was the change in serum uric acid concentration. Secondary analyses of efficacy were based on changes in renal function, blood pressure and other haematological and urinary parameters.

Methodology

At each clinic visit, blood pressure (SBP and DBP) was recorded in the resting position as the average of two duplicate readings made at intervals of 3 min using a regular mercury sphygmomanometer. Serum and urine measurements of uric acid were made colorimetrically using uricase. CsA was determined by the enzyme-multiplied immunosassay technique (Behring Diagnostics, France). Other electrolytes were measured by routine clinical chemistry methods.

Renal function was assessed at the end of the placebo run-in period (day 0), before any medication was administered, and at day 60 using measures of clearance rates. The evening (10.00 p.m.) before each assessment, the study participants were given 300 mg lithium carbonate orally. The following morning, after fasting for 12 h, the patients attended the laboratory at 8.00 a.m. They received 200 ml water every 30 min throughout the study to maintain constant urine production. After urine voiding, the patients were maintained in the supine position. Two catheters, one in each arm, were inserted for blood sampling and the administration of the tracers, inulin and p-aminohippuric acid (PAH). At 9.00 a.m., a priming dose of 0.16 ml × weight of inulin 10% (Inutest-Ampullen; Isotec, St Quentin, France) and 0.036 × weight of PAH 20% (Nephrotest; Isotec, St Quentin, France) was given intravenously, followed by the continuous infusion of inulin and PAH in isotonic saline to the end of the study. This infusion was administered at the appropriate rate required to provide a constant plasma concentration of inulin and PAH (three to five times the background), taking into account the estimated clearance value of the study participant. Blood samples were drawn every hour. Allowing 1 h for equilibration, urine was collected every hour for three consecutive clearance measurements of the three tracers (inulin, PAH and lithium).

The continuous infusion technique outlined above was used for determination of renal plasma flow (RPF) and GFR. GFR was determined as the inulin clearance and RPF was determined from the PAH clearance (C_{PAH}) by applying the formula:

\[ \text{RPF} = \frac{C_{PAH}}{1 - Ht} \]

where Ht is the haematocrit.

Lithium was measured by atomic absorption spectrometry. Segmental tubular function was determined using the lithium clearance technique, which assumes that lithium is reabsorbed in the proximal tubule to the same extent as sodium and water and that lithium is neither secreted nor reabsorbed in the distal nephron. Thus, lithium clearance (C_{Li}) equals the output of isotonic fluid from the proximal tubule. With the use of GFR, C_{Li}, clearance of sodium (C_{Na}) and concentration of sodium in plasma (P_{Na}), the following parameters could be calculated.
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Absolute proximal reabsorption of sodium
\[(\text{APR}_{\text{Na}}) = (\text{GFR} - \text{CLi}) \times P_{\text{Na}})\]

Fractional proximal reabsorption of sodium
\[(\text{FPR}_{\text{Na}}) = (1 - \frac{\text{CLi}}{\text{GFR}}) \times 100\]

Absolute distal reabsorption of sodium
\[(\text{ADR}_{\text{Na}}) = (\text{CLi} - \text{CNa}) \times P_{\text{Na}})\]

Fractional distal reabsorption of sodium
\[(\text{FDR}_{\text{Na}}) = (\frac{\text{CLi} - \text{CNa}}{\text{CLi}}) \times 100\]

Clearance of uric acid (CUA) and electrolytes was measured from 24 h urine collections. Fractional clearance refers to crystalloid clearance divided by GFR. All these parameters were standardized to a body surface of 1.73 m².

Safety evaluation

The safety of both amlodipine and tertatolol was evaluated by the occurrence of adverse events (AEs), serious adverse events (SAEs) and premature discontinuation from the study. All AEs observed by the investigator or reported by the patient were recorded and were classified by body system and preferred terms, using the World Health Organization’s Adverse Reaction Terminology dictionary. SAEs were considered events leading to death, hospitalization or significant disability.

Statistical methods

An estimated sample size of 50 patients (25 per group) was required to detect a difference in serum uric acid concentration of 80 ± 100 μmol/l between treatments, with a power of 80% and a significance level of \(P = 0.05\) (two-tailed). Statistical analysis was performed on the intent-to-treat (ITT) population, which consisted of all randomized patients who took at least one dose of the study treatment during the double-blind period of the study and had at least one measurement available for the required analysis.

The type of descriptive analysis chosen was dependent on the nature of the variables. Quantitative variables were expressed as means ± SD (normal distribution) or as medians and first and third quartiles (non-normal distribution). Treatment group comparability in terms of baseline measurements was analysed using \(\chi^2\) test or Fisher’s exact test for qualitative variables and Student’s t-test or Wilcoxon test for quantitative variables, according to their statistical distribution. Efficacy parameters measured at days 0, 15, 30 and 60 were compared between treatment groups using a two-way analysis of variance (ANOVA) for repeated measurements. In the case of a significant interaction effect, a one-way ANOVA for repeated measurements was performed on each treatment group. Renal function parameters, measured at days 0 and 60, were compared between the two treatment groups using either a Mann–Whitney test or a Student’s t-test, depending on their statistical distribution. All tests were two-tailed, using a fixed level of significance at \(P < 0.05\).

Results

Study population

Of the 53 patients initially selected for study, five were withdrawn from randomization because of AEs (\(n = 2\)) or because of a normal blood pressure reading at inclusion (\(n = 3\)). Thus, 48 hypertensive renal transplant patients (69% male; mean age: 46.7 ± 10.7 years) treated with CsA were randomized to receive at least one dose of either amlodipine (\(n = 24\)) or tertatolol (\(n = 24\)). These 48 patients constituted the ITT population for statistical analysis.

Baseline characteristics of the study participants are given in Table 1. Both treatment groups were comparable. No significant difference was observed between groups for any baseline values of efficacy parameters and there was no significant difference between treatment groups regarding the frequency of concomitant treatments or disease at inclusion. In addition, there was no difference between treatment groups for any other demographic criteria – only the patient’s previous medical history and the mean time since the renal transplant were at the limit of statistical significance (\(P = 0.051\)). The former was believed to be because six amlodipine patients, but no tertatolol patients, had experienced organ rejection prior to the study. However, all between-group differences were statistically determined to have no influence on the significance of the efficacy results.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amlodipine ((n = 24))</th>
<th>Tertatolol ((n = 24))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males:females</td>
<td>17:7</td>
<td>16:8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.2 ± 9.9</td>
<td>48.2 ± 11.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.1 ± 12.9</td>
<td>65.7 ± 11.8</td>
</tr>
<tr>
<td>Time since transplantation (months)</td>
<td>53.0 (Q1 11.0; Q3 88.5)</td>
<td>15.5 (Q1 9.0; Q3 36.0)</td>
</tr>
<tr>
<td>Time hypertensive (months)</td>
<td>57.7 ± 52.0</td>
<td>82.0 ± 97.8</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>151.2 ± 11.9</td>
<td>153.5 ± 12.3</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>94.3 ± 7.7</td>
<td>92.9 ± 7.9</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>129.8 ± 37.0</td>
<td>127.3 ± 28.1</td>
</tr>
<tr>
<td>CsA dosage (μg/l)</td>
<td>125.9 ± 54.2</td>
<td>121.5 ± 28.0</td>
</tr>
</tbody>
</table>

In all parameters, no significant differences were observed between treatment groups. Values are means ± SD, except time since transplantation, which is expressed as the median value plus the first and third quartile (Q).
Treatment compliance was high in the amlodipine (96.7%) and tertatolol (92.7%) groups and did not differ significantly. The daily treatment dose was doubled (from 5 to 10 mg) in eight patients (17%): three (12.5%) amlodipine patients and five (20.8%) tertatolol patients. The Fisher’s exact test showed no significant difference between treatment groups.

Serum levels of uric acid

The mean levels of serum uric acid were comparable in the amlodipine (482.5 ± 98.7 μmol/l) and tertatolol (449.7 ± 98.1 μmol/l) treatment groups at baseline. However, the time-dependent profile of changes in the serum levels of uric acid was statistically different ($P < 0.001$) between the two treatment groups (Figure 1). While uric acid levels significantly decreased from baseline in the amlodipine group to 430.9 ± 109.5 μmol/l ($P < 0.001$), levels of serum uric acid increased significantly from baseline in the tertatolol group to 475.9 ± 84.0 μmol/l ($P = 0.006$).

Renal function

The descriptive and analytical results for the various determinants of renal function are given in Table 2. Following 60 days treatment, the clearance rate of uric acid was significantly increased by amlodipine compared with tertatolol therapy ($P = 0.023$). In addition, GFR, as determined by inulin clearance, showed a significant difference between the treatment groups ($P = 0.0048$). Amlodipine increased the GFR, whereas tertatolol treatment decreased it. There was no difference in RPF, filtered fraction or the fractional excretion of uric acid between the two treatment groups, despite a tendency for these parameters to increase in the amlodipine group. Amlodipine treatment also significantly increased the clearance rate of lithium, compared with tertatolol therapy (Table 2). Concurrently, amlodipine treatment significantly decreased FPR$_{Na}$ and significantly increased ADR$_{Na}$ and FDR$_{Na}$, compared with tertatolol.

Serum creatinine was significantly lower after 60 days treatment with amlodipine, compared with baseline levels (119.6 ± 37.6 vs 129.8 ± 37.0 μmol/l; $P < 0.001$). There was no significant change in serum creatinine in the tertatolol group.

Blood pressure

At day 30, blood pressure remained high (DBP between 90 and 110 mmHg and/or SBP between 140 and 180 mmHg) in eight patients (17.02%): three (12.50%) amlodipine patients and five (21.74%) tertatolol patients. Accordingly, the daily dose of both drugs was doubled from 5 to 10 mg in these subjects. There was no significant difference between treatment groups regarding the frequency of titration at day 30.
Both amlodipine and tertatolol significantly decreased SBP and DBP throughout the study (Figure 2). However, by day 60, the decrease in SBP was significantly greater ($P = 0.007$) in the amlodipine group (day 0: 151.2 ± 11.9 mmHg; day 60: 131.5 ± 10.4 mmHg) compared with the tertatolol-treated patients (day 0: 153.5 ± 12.3 mmHg; day 60: 148.4 ± 18.7 mmHg). The time-dependent profile of DBP did not differ significantly between treatment groups.

**Safety**

Twelve of the 24 patients receiving tertatolol and 13 of the 24 patients receiving amlodipine presented with one or more AEs during the study. Among the AEs, only 15 were considered by the investigators to be drug-related, including eight in the amlodipine group (leg oedema and extrasystoles) and seven in the tertatolol group (fatigue, headache or hot flushes). These rates were not significantly different between the two treatment groups (Fisher’s exact test: $P = 0.385$).

Only one patient, in the tertatolol group, discontinued the trial because of an AE (bradycardia) and no SAEs occurred during the study.

**Discussion**

This comparative, double-blind study shows that amlodipine (5–10 mg/day) and tertatolol (5–10 mg/day) have opposing effects on CsA-induced hyperuricaemia in hypertensive renal transplant recipients. Amlodipine therapy significantly decreased serum levels of uric acid, whereas serum uric acid levels were increased following an equivalent period of tertatolol treatment. Furthermore, amlodipine lowered SBP to a significantly greater extent than did tertatolol and produced improvements in several parameters of renal function not replicated in the tertatolol treatment group. Both drugs were well tolerated. These results suggest that amlodipine may be a more appropriate antihypertensive treatment than tertatolol in CsA-treated renal transplant patients.

Though CsA improves renal allograft survival after transplantation, experimental and human studies have documented that CsA acutely reduces GFR [3]. This may be a direct tubular effect, due to CsA increasing intrarenal vascular resistance. The consequent decrease in the excretion of uric acid results in hyperuricaemia, a common complication of CsA therapy [5]. Hyperuricaemia may, itself, exacerbate chronic CsA nephropathy [11].

The efficacy of amlodipine, compared with tertatolol, in reducing hyperuricaemia (and serum levels of creatinine) in the present study may be explained by their differential action on renal function. Amlodipine therapy increased the GFR and, consequently, the clearance rates of uric acid and creatinine. Furthermore, amlodipine treatment increased the output of fluid from the proximal tubules, as demonstrated by the significant decrease observed in the fractional proximal reabsorption of sodium and the corresponding increase in the reabsorption of sodium in the distal tubule.

It has been previously reported that calcium channel blockade can partially prevent CsA-induced renal dysfunction. In a 24 month study of 253 normotensive and hypertensive renal transplant recipients, the CCB, nitrendipine, was found to provide protection against CsA-induced deterioration of renal function [12]. Patients treated with nitrendipine had lower serum creatinine concentrations at the end of treatment than patients in the placebo group. In addition, once daily treatment with amlodipine has previously been found to be at least as effective as twice daily nifedipine (another dihydropyridine CCB) in controlling blood pressure and increasing GFR in hypertensive renal transplant patients [9]. The efficacy of amlodipine, compared with the ß-blocker tertatolol, in reducing hyperuricaemia (and serum levels of creatinine) in the current study corroborates the beneficial action of this CCB on renal function.

Several CCBs are known to inhibit the metabolism of CsA and thereby increase blood CsA concentrations [1]. The potential toxicity arising from elevated blood
CsA may offset the beneficial effects of calcium channel blockade. However, several studies have suggested that amlodipine may not alter the pharmacokinetics and, thus, levels the CsA [8]. The results of the current study support these studies – trough levels of CsA did not change significantly during the 60 day study period in either the amlodipine or tertatolol treatment groups.

Despite equivalent dosage and rates of titration in the current study, tertatolol treatment did not lower SBP as effectively as amlodipine. In addition, tertatolol had a deleterious influence on renal function, significantly decreasing GFR and increasing serum uric acid levels. Only one other study has previously examined the renal haemodynamic effects of tertatolol in hypertensive renal transplant patients on CsA [13]. This shorter study (4 weeks) in only 12 patients reported that tertatolol had a neutral influence on renal function. However, negative results similar to the present study have been observed with other β-blockers in long-term studies. For example, the β-blocker propranolol, given in the short and long term, lowers both RPF and GFR [14]. β-Blockade with atenolol in patients with mild to moderate essential hypertension produced a significant decrease in RPF and uric acid clearance [15]. Combined, these findings suggest that β-blockers may not constitute the optimal management of CsA-induced hypertension and nephropathy in renal transplant patients.

The benefit in renal haemodynamics and, thus, reduction in hyperuricaemia afforded by amlodipine also compares favourably with that of other vasodilatory therapies. In one 4 week study, treatment with amlodipine, compared with the ACE inhibitor, lisinopril, increased GFR and RPF and reduced renal vascular resistance [16]. A further study showed that 8 week treatment with amlodipine was more effective than the ACE inhibitor, perindopril, in lowering serum levels of uric acid and increasing uric acid clearance, despite similar levels of blood pressure control [10].

It has previously been suggested that the angiotensin II AT1 receptor antagonist, losartan, had a uricosuric effect in patients with renal transplants, increasing the fractional excretion of uric acid [17]. However, the estimate of uric acid excretion was based solely on data from 24 h urine collections rather than the vigorous renal function tests employed in the present study. Indeed, a recent trial comparing the effects of amlodipine and losartan on renal haemodynamics in CsA-treated renal transplant patients revealed that only amlodipine increased GFR, while losartan reduced the estimated glomerular hydrostatic pressure and filtration fraction [18].

It remains to be elucidated whether the potential renal protective effects of amlodipine treatment result directly from its influence on the kidney or indirectly via its effective control of blood pressure. Amlodipine has been shown to increase GFR in normotensive orthotopic liver transplant recipients with CsA-induced renal impairment, after only 3 weeks of treatment [19]. In another study, amlodipine significantly reduced serum levels of creatinine in normotensive renal transplant patients, in the absence of marked changes in blood pressure [20]. The small but significant nephroprotective effects of the CCB nitrendipine, recorded in hypertensive renal transplant patients, were independent of its antihypertensive effects; blood pressure values at the end of the 24 month study were similar in nitrendipine-treated and placebo groups [12].

High serum levels of uric acid are the key risk factor for the development of arthritic gout. In a review of several studies, ~80% of renal transplant recipients receiving CsA were observed to be hyperuricaemic and almost 10% of these individuals developed gout [6]. Given the efficacy of amlodipine in reducing hyperuricaemia in the current study, these data provide the rationale for a randomized clinical trial of amlodipine for the prevention of gout in hypertensive renal transplant patients treated with CsA.

In conclusion, once daily amlodipine significantly increased the urinary elimination of uric acid in hypertensive renal transplant patients with CsA-induced hyperuricaemia, compared with the non-selective β-blocker, tertatolol. In addition, amlodipine was more effective as an antihypertensive agent and was well tolerated. These results suggest amlodipine may be considered a more appropriate treatment than tertatolol for concomitant administration with CsA.

Conflict of interest statement. C. Bernaud holds stock in Pfizer, the makers of amlodipine, and is currently conducting research sponsored by this company. All other authors declared no conflict of interest.

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