Renal and systemic effects of atenolol and tertatolol in renal transplant recipients on cyclosporine A

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Abstract

Background. Hypertension and nephrotoxicity are well-known side-effects of cyclosporine A (CsA). CsA-induced vasoconstriction of the afferent glomerular arteriole probably plays a role in at least the nephrotoxicity. Frequently renal transplant recipients on CsA have to be treated with antihypertensive drugs and for this purpose also β-blockers are used. Tertatolol is a new β-blocker with specific vasodilatory properties, and thus might be particularly useful in CsA-treated transplant recipients.

Methods. We studied the systemic and renal haemodynamic effects of atenolol and tertatolol in 12 hypertensive renal transplant recipients on cyclosporine A (CsA). In a cross-over way, all patients were treated with atenolol and tertatolol for 4 weeks each, separated by a wash-out period also of 4 weeks. At the end of each period, the mean arterial pressure (MAP), heart rate, glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured.

Results. The mean arterial pressure was lower (P<0.05) during atenolol (124±2 mm Hg) and tertatolol (125±2 mm Hg) treatment compared with wash-out (132±4 mm Hg). Also the heart rate was lower (P<0.01) during atenolol and tertatolol (54±3 and 55±2 beats/min respectively) than in the wash-out period (65±3 beats/min). GFR and RPF were not changed by either β-blocker.

Conclusion. In CsA treated renal transplant recipients both atenolol and tertatolol effectively reduced blood pressure. In these patients we found no evidence of a specific vasodilatory effect of tertatolol. Both β-blockers had no negative influence on renal function. Hence, these cardioprotective agents are an attractive and safe choice for the treatment of hypertension in such patients.

Key words: hypertension; transplantation; cyclosporine A; β-blockers; renal haemodynamics
Subjects and methods

Patients

The study was approved by the hospital Ethics Committee and all patients gave written informed consent before study entrance. Hypertensive renal transplant recipients (n = 12) on CsA, already using atenolol, were recruited from our transplant population. The characteristics of the 12 participants are presented in Table 1. In the seven patients treated with a combination of antihypertensive agents, all antihypertensive drugs except atenolol were withdrawn at least 4 weeks before the start of the study. All participants had stable renal transplant function with a calculated Cockcroft creatinine clearance of at least 30 ml/min and stable CsA trough levels during the last 3 months preceding the study. The patients varied in original kidney diseases (two primary focal glomerulosclerosis, two undefined glomerulonephritis, three polycystic kidney disease, three chronic pyelonephritis, and two kidney diseases of unknown origin). Both native kidneys were still in situ in all patients except in one who had undergone unilateral nephrectomy before transplantation. As immunosuppressive regimen three patients used CsA monotherapy and nine used CsA in combination with prednisone in a daily dose of 11 ± 2 mg (range 10–15 mg).

Study design

This open study consisted of three consecutive treatment periods of 4 weeks each, all periods ending with a renal function measurement. In the first 4 weeks patients were treated with atenolol 100 mg once daily, a dose equipotent to 5 mg of tertatolol. Hereafter, a wash-out period was scheduled. In 1 week the atenolol dosage was tapered to zero. This was followed by a 3 week period without any antihypertensive treatment. The last 4 weeks the patients were treated with tertatolol 5 mg once daily. Patients were advised to take the β-blockers every morning at breakfast time.

Renal function measurement

Renal function measurements were performed in the morning from 9.00 am until 2.00 pm. The patients were instructed to refrain from smoking and coffee drinking during the last 8 h and from alcohol during the last 24 h before the renal investigations. The daily dose of the β-blocker was already taken at home at breakfast and the morning dose CsA was administered in the ward after the first blood sample had been drawn. A venous catheter was inserted in the forearm for continuous infusion of an inulin (polyfructosan; Inutest, Laeovsan Gesellschaft, Linz, Austria) and para-amino-hippuric acid (PAH)-solution, as described before [13]. After a 90 min equilibration period three clearance periods of 45 min each were scheduled. Blood and urine samples were collected at the beginning and end of the clearance periods. The patients remained supine except for spontaneous voiding. Mean arterial pressure (MAP) and heart rate (HR) were monitored every 5 min with an automatic device (Dinamap, Critikon, FL, USA). During the measurements, diuresis was maintained by an oral water load of 150 ml per 30 min.

Laboratory procedures

PAH, inulin and creatinine concentrations in urine and plasma samples were determined by standard techniques and haematocrit was determined by routine Coulter counter. Whole blood CsA levels were measured with a monoclonal antibody against the CsA parent molecule (Abbott TDX, Abbott Laboratories, Chicago, USA).

Calculations and statistical analysis

GFR was estimated by inulin clearance and effective RPF by PAH clearance. Plasma concentrations (P), urine concentrations (U) and urine flow (V) were used to calculate the clearances (Cl) of both substances according to the standard formula Cl = UV/P. Filtration fraction (FF) was calculated by GFR/RPF. Mean values of the three clearance periods were used for further analysis. All values were adjusted to a standard body surface area of 1.73 m². Mean arterial pressure and heart rate were calculated as the mean of five Dinamap recordings in the middle of each clearance period. All values are expressed as means ± SEM unless stated otherwise. Statistics were performed with the SAS system (SAS Institute Inc, Cary, NC, USA). To compare the renal and systemic haemodynamic results of the three treatment periods two-tailed paired Wilcoxon tests were used. P < 0.05 was considered to be statistically significant.

Results

During the wash-out period (without antihypertensive treatment) systolic blood pressure and diastolic pressure by mercury sphygmomanometry were respectively 160 ± 5 mm Hg and 106 ± 3 mm Hg, the heart rate was 68 ± 2 beats/min. The haemodynamic parameters as measured during the three study periods are given in Table 2. In comparison with the wash-out period heart rate was lower during treatment with both atenolol and tertatolol (P < 0.01). MAP was also lower during treatment with both β-blockers (P < 0.05). Although blood pressure was lower during treatment with the β-blockers, both GFR and RPF were maintained at the same level as during wash-out. Specifically, there was no evidence of a more pronounced vasodilation during the use of tertatolol. Although the number of patients is small, we analysed the antihypertensive efficacy of the β-blocker according to the original renal disease.
The four patients with glomerulonephritis as their original kidney disease had a higher MAP during the wash-out period than the patients with other kidney diseases (141 ± 2 mm Hg vs 120 ± 1 mm Hg). They also showed a more striking decrease in MAP during β-blockade (mean decline 14 ± 2 mm Hg in the glomerulonephritis group vs 3 ± 1 mm Hg in the remaining group, P < 0.01). There was no apparent pharmacokinetic interaction between the β-blockers and CsA since whole blood CsA trough levels remained stable during the whole study period. The means of these trough levels were 187 ± 33 and 160 ± 40 ng/ml during treatment with atenolol and tertatolol respectively, and 152 ± 48 ng/ml during the wash-out period.

### Discussion

In our transplant recipients on CsA, both atenolol and tertatolol effectively reduced blood pressure without negatively influencing renal function. This makes these drugs with their well-known cardioprotective effects [14] an attractive choice for this category of patients with a high prevalence of cardiovascular disease. To the best of our knowledge, this effectiveness of β-blockers in renal transplant recipients on CsA has not been clearly demonstrated before and could seem somewhat surprising in view of the limited role of the renin–angiotensin system (RAS) in CsA-induced hypertension in humans. In contrast to animal studies, CsA administration in animals does not stimulate the RAS and even can suppress it [1]. Increased sympathetic nerve activity and increase of intravascular volume seem to play a more important role in CsA-induced hypertension [15].

Our study does not allow a conclusion on superiority of tertatolol over atenolol in CsA treated hypertensive patients, since the effects of both drugs were comparable. Of note, we did not find any indication for a renal vasodilatory effect of tertatolol in these patients in contrast to other observations with this drug in both patients with essential hypertension and patients with moderate renal failure [10–12]. In these previous studies it was suggested that in addition to its β-blocker properties tertatolol had specific vasodilatory effects operating at both the afferent and efferent arteriole, causing an increase in GFR and RPF without influencing filtration fraction. The mechanisms of the vasodilatory property of tertatolol are unclear and remarkable in view of the mode of action of tertatolol which as a non-selective β-blocker also blocks vasodilating β2-adrenoceptors. However, although the presence of β2-adrenoceptors in renal vessels has been demonstrated, their impact of influence on renal blood flow regulation seem to be of minor importance [8]. In a previous study it was suggested that β-receptor blockade is not directly involved in the renal vasodilator effects of tertatolol because dissociations were observed between changes in plasma renin activity and plasma aldosterone, and the increase of renal blood flow [12]. Plasma renin activity and plasma aldosterone both decreased early after tertatolol infusion, whereas the increase in renal blood flow was delayed. Furthermore, the results of studies using rat kidneys suggest that the renal vasodilation caused by tertatolol is related to its agonistic action on 5-HT1A receptors [16,17]. Intervention studies measuring the effects of CsA revealed various mediators which have been considered to be of importance in CsA induced hypertension. However, in these studies the vasoconstrictor effects of CsA could not be clarified completely since only partial improvement in renal haemodynamics was achieved [18]. Whatever the mechanisms of both drugs are, from our data it is evident that tertatolol is not able to attenuate the vasoconstrictor effect of CsA. At first sight, our data also seem to be in contrast to the observations with carvedilol in a comparable group of renal transplant recipients [19]. In that study, the β1-selective agent metoprolol and the non-selective carvedilol had comparable effects on blood pressure but only carvedilol induced renal vasodilation. However, this renal effect could be easily explained by the β2-adrenoceptor blocking property of carvedilol which is lacking in tertatolol.

Despite the effectiveness of β-blockers as shown in the present study, CEBs still are the best suitable drugs in the treatment of CsA induced hypertension in patients on CsA. Besides their blood pressure lowering effects, CEBs counteract the CsA induced reduction of GFR and RPF and acutely even cause natriuresis during the use of CsA [6,20]. These favourable effects of CEBs during CsA are to be ascribed to their vasodilatory action on resistance arterioles, and, with respect to their renal actions, largely on the specific vasodilation of afferent arterioles. When combing CsA and a calcium entry blocker one must realize that some CEBs interfere with the metabolism of CsA, thus necessitating a CsA-dose reduction [21]. Other important problems during treatment with CEBs are their earlier mentioned side-effects. Indeed, many of these side-effects, such as palpitations and headache, can be counteracted by β-blockers. This means that β-blockers are not only suitable as monotherapy but also very useful in combination with CEBs.

Although the present study does not allow firm conclusions due to the low number of patients, the data seem to confirm our previous studies [22,23] in which we demonstrated that the antihypertensive effi

### Table 2. Results of mean arterial pressure (MAP), heart rate (HR) and renal function assessment during three consecutive treatment periods. Values shown are means ± SEM

<table>
<thead>
<tr>
<th></th>
<th>Atenolol</th>
<th>Washout</th>
<th>Tertatolol</th>
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<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>124 ± 2*</td>
<td>132 ± 4</td>
<td>125 ± 2*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>54 ± 3*b</td>
<td>65 ± 3</td>
<td>55 ± 2*b</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>45 ± 3</td>
<td>47 ± 4</td>
<td>45 ± 3</td>
</tr>
<tr>
<td>RPF (ml/min/1.73 m²)</td>
<td>167 ± 15</td>
<td>163 ± 14</td>
<td>158 ± 11</td>
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*P < 0.05 and *P < 0.01 compared with wash-out.

GFR = glomerular filtration rate; RPF = renal plasma flow.
cacy of β-blockers was more pronounced in patients with glomerulonephritis as their original disease than in patients with other renal diseases. Previously, we and others have demonstrated that native kidneys play a major role in sustaining hypertension in renal transplant recipients. The role of the native kidneys is probably mediated by an inappropriately high renin secretion [22,24]. This hypothesis as well as the present data are in agreement with studies showing a larger antihypertensive effect of β-blockers in patients with high renin levels [25].

In conclusion, in renal transplant recipients on CsA, the β-blockers atenolol and tertatolol are effective antihypertensive drugs that do not compromise renal function and especially not renal perfusion. Compared with atenolol, tertatolol did not have a favourable influence on renal function. Thus, the potential vasodilatory effects of tertatolol are out weighed by the vasoconstrictory potential of CsA, β-blockers as monotherapy or combined with other antihypertensive drugs, seem to be a good choice for the treatment of hypertensive renal transplant recipients on CsA.

References

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