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Detailed study of changes in renal function after conversion from cyclosporine to azathioprine

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Abstract. The renal dysfunction induced by cyclosporine (CsA) has been demonstrated to be at least partially reversible after cessation of CsA therapy. The time course and magnitude of changes in various parameters of renal function after CsA withdrawal have not been studied in detail. We examined 12 renal transplant patients immediately before and 1, 2, and 4 weeks after replacement of CsA by azathioprine at 3 months after transplantation. Nine patients in whom CsA was continued during this period served as a control group. A significant increase in glomerular filtration rate ([GFR] 15 ± 17%, p < 0.01) occurred already in the first week after discontinuation of CsA. From 1 to 4 weeks after conversion, GFR did not significantly increase any further. A fall in serum creatinine (-7 ± 9%, NS) paralleled the rise in GFR (r = -0.76, p < 0.01), but there was a further decrease of creatinine in the second to fourth week after conversion. Withdrawal of CsA induced a rise in serum magnesium in all patients (0.73 ± 0.13 vs 0.86 ± 0.12 mmol/l, p < 0.001) as well as a marked decrease in the serum level of urate (0.39 ± 0.09 vs 0.33 ± 0.07 mmol/l, p < 0.01) within one week. None of the observed changes took place in the control group. In conclusion, a major improvement of GFR occurs within one week after cessation of CsA therapy. Changes in the serum levels of magnesium and urate appear to be the most responsive markers of the renal effects of CsA.

Key words: renal function - renal transplantation - cyclosporine - conversion

Introduction

The immunosuppressive drug cyclosporine A (CsA) contributes greatly to the successful treatment of transplant recipients and patients with auto-immune diseases. An important side effect of CsA is the impairment of renal function. Although long-term use of the drug may result in irreversible renal injury, discontinuation of CsA is usually followed by considerable recovery of renal function [Chapman et al. 1985]. This reversible component of CsA-induced renal dysfunction has been ascribed to preglomerular vasoconstriction [Conte et al. 1989, Sabbatini et al. 1993], a functional effect that should cease immediately after CsA withdrawal. Several human studies provide information on the degree of improvement in creatinine clearance or glomerular filtration rate (GFR) that can be expected after cessation of CsA [Chapman et al. 1985, Versluis et al. 1987]. However, comprehensive data on the time course of these changes are not available. We therefore performed a prospective study to examine the rate of changes in renal function during the first four weeks following conversion from CsA to azathioprine at three months after renal transplantation. In addition to GFR, various other indices of renal function (such as tubular handling of sodium and uric acid) were measured in order to identify the most sensitive markers of the renal effects of CsA.

Methods

Subjects

The study group consisted of 12 renal transplant patients (10 M, 2 F; age 41 ± 14 years) in whom elective conversion from CsA to azathioprine was carried out at three months after transplantation as part of another study protocol (randomized prospective trial comparing conversion from CsA to azathioprine with CsA monotherapy from three months after renal transplantation). Nine patients (7 M, 2 F; age 42 ± 12 years) who were allocated to continuation of CsA served as the control group. Patients were eligible for this study if renal function was stable (variation in serum creatinine of less than 15% in two weeks prior to the study) and diastolic blood pressure was below 110 mmHg. Patients who were using diuret-
Changes in renal function after conversion from CsA to azathioprine

ics, xanthine derivatives, or nonsteroidal anti-inflammatory drugs were excluded. Furthermore, two patients were excluded during the four-week study period because an acute rejection episode was diagnosed (the study and control population initially consisted of 13 and 9 patients respectively). During the first three months after transplantation, immunosuppressive treatment consisted of CsA (initial oral dose of 12 mg/kg/d, tapered to approximately 4 mg/kg/d in two divided doses) and prednisone (20 mg/d at the time of the study) in all patients. In the conversion group, CsA was replaced by azathioprine in a dosage of 3 mg/kg/d. The prednisone dosage was temporarily increased from 20 to 25 mg/d during the first two weeks after conversion but was back on 20 mg/d during the following two weeks. In patients who continued on CsA, the dose of CsA was not changed and according to our treatment protocol, the prednisone dosage was reduced from 20 to 10 mg/d during the four-week study period. Six patients (4 in the conversion group and 2 in the control group) used atenolol (50 to 100 mg once daily) and 11 patients (4 in the conversion group and 7 in the control group) received the combination of atenolol and nifedipine (10 or 20 mg slow release tablets twice daily) as antihypertensive therapy. The dose of these drugs was not changed during the study period. The study was approved by the Hospital Ethics Committee and all patients gave written informed consent.

Study protocol

In the conversion group, measurements were carried out on the day before discontinuation of CsA (at three months after transplantation) and 1, 2, and 4 weeks afterwards. Patients in the control group underwent the same measurements only at the first and last occasion of this series, i.e. at 3 and 4 months after transplantation. All experiments were performed from 9:00 a.m. till noon. The patients were on a regular diet but were advised to avoid the use of coffee, alcohol, liquorice, or tobacco during the last nine hours preceding the measurements. The evening preceding each experiment, 300 mg of lithium carbonate (8.1 mmol of lithium) was given orally. A light breakfast on study days was allowed and if applicable, antihypertensive drugs were taken with breakfast. Upon arrival in the ward, a blood sample was drawn for determination of the CsA trough level. Immediately thereafter, the patients ingested their regular morning dose of CsA. A sufficient diuresis was attained by an initial oral water load of 10 ml per kg body weight, followed by i.v. infusion of a solution of 0.25% NaCl (to compensate for expected sodium losses in the urine) in 3.3% glucose at a rate of 400 ml/h. Urinary fluid losses in excess of the infused volume were replaced orally by tap water. Except for spontaneous voiding in upright position, patients remained supine.

Gomorular filtration rate (GFR) and renal plasma flow (RPF) were measured using a continuous infusion technique. Renal clearances of inulin (polyfructosan, Inustest®; Luevusan-Gesellschaft, Linz, Austria) and paraaminohippuric acid (PAH) were used as markers of GFR and RPF, respectively. After an equilibration period of 90 min, urine was collected at 30 min intervals. Blood samples were drawn at the midpoint of each urinary collection period. Blood pressure and heart rate were recorded every three minutes with an automatic device (Dinamap model 1846P, Critikon Inc., Tampa, FL, USA). The mean values of five consecutive readings around the midpoint of each clearance period were used for analysis.

The filtration fraction (FF) was calculated as GFR/RPF × 100% and renal blood flow (RBF) was estimated using the formula RBF = RPF/(1 - haematocrit). Renal vascular resistance (RVR) was defined as mean arterial pressure (MAP) divided by RBF and expressed in arbitrary units. Fractional excretions of sodium and uric acid (FE\text{Na} and FE\text{Ur}) were calculated as their respective renal clearances (C\text{Na} and C\text{Ur}) divided by GFR and expressed as percentage. Using the lithium clearance (C\text{Li}) as an approximate marker of proximal tubular sodium and water reabsorption [Thomsen 1984, Boer et al. 1995], the fractional proximal sodium reabsorption (FPR\text{Na}) and fractional distal sodium reabsorption (FDR\text{Na}) were estimated by the following calculations:

\[
\text{FPR}\text{Na} = (1 - \text{C}\text{Li}/\text{GFR}) \times 100\% \\
\text{FDR}\text{Na} = (1 - \text{C}\text{Na}/\text{C}\text{Li}) \times 100\%.
\]

Clearances of the various parameters were calculated for each of the three 30 min intervals and these values were averaged subsequently. The resulting clearance values were adjusted to a standard body surface area of 1.73 m².

Analytical procedures

In serum or urine samples, PAH, inulin, creatinine, sodium, potassium, magnesium, uric acid, and bicarbonate were measured by standard techniques. Lithium was determined by atomic absorption spectrophotometry. In blood samples the hematocrit was determined by routine Coulter counter and whole blood CsA levels were measured with a monoclonal antibody against the CsA parent molecule using Abbott TDX (Abbott Laboratories, North Chicago, IL, USA).

Statistical analysis

Data are reported as means ± SD unless stated otherwise. Results were analyzed with Wilcoxon's test for paired or unpaired observations when appropriate.
Correlations were assessed by calculating Spearman’s correlation coefficient. A probability value less than 0.05 was considered statistically significant. No correction for comparison of multiple outcomes was applied.

Results

Base-line values of blood pressure, renal hemodynamic parameters, and other indices of renal function did not differ between the conversion and control group (Tables 1 and 2). There were no differences between patients who used atenolol as the sole antihypertensive drug (n = 6) and patients without antihypertensive therapy (n = 4) with respect to base-line values of the parameters given in Tables 1 and 2. However, when all patients who used nifedipine (n = 11) were compared to those who did not (n = 10), the former group was characterized by a higher FENa (6.5 ± 2.8% vs 3.3 ± 0.8%, p <0.01), a lower FPRNa (53.2 ± 11.3% vs 66.6 ± 7.1%, p <0.01), and a lower FDRNa (86.4 ± 4.1% vs 90.0 ± 2.1%, p <0.05) at week 0. In the control patients, who continued to use CsA, the CsA trough levels remained constant (week 0: 161 ± 48 ng/ml, week 4: 176 ± 52 ng/ml; NS). Patients in the conversion group had similar CsA levels at week 0 (176 ± 59 ng/ml; NS for difference versus control group).

One week after discontinuation of CsA, GFR had improved in all but one patient. During the next three weeks, a slight and statistically non-significant further increase in GFR was observed (Table 1). After four weeks, the change in GFR in the conversion group significantly differed from that in the control group. RPF and RVR showed an increase and decrease respectively, but statistical significance was not achieved for the difference with the control group. Conversion from CsA to azathioprine was not followed by a change in the filtration fraction (0.22, 0.20, 0.20, and 0.22 at 0, 1, 2, and 4 weeks respectively). A fall in serum creatinine during the first week after conversion was followed by a further decrease during the subsequent 3 weeks, resulting in a significant difference from base-line from 2 weeks after conversion. At 1 and 4 weeks after conversion, serum creatinine had decreased in 9 and 11 of all 12 cases respectively. Blood pressure tended to decline after CsA withdrawal, although the difference did not reach statistical significance.

The time course of other potential indices of the renal effects of CsA are given in Table 2. The most common change during the first week after conversion was a rise in the serum magnesium level, which occurred in all patients. In addition, there was a rapid and marked decrease in the serum level of urate. The fractional excretion of uric acid did not change after conversion from CsA to azathioprine (17 ± 8% at base-line vs 16 ± 8% at 4 weeks). There was a slight decrease in FENa which appeared to be due to an increase in the fractional distal reabsorption of sodium. However, as mentioned above, tubular handling of sodium and lithium were influenced by the use of nifedipine. To circumvent this potential source of bias, we repeated the analysis on tubular sodium handling after exclusion of 4 nifedipine users from the conversion group. As is shown in Table 3, in the

Table 1  Blood pressure, renal hemodynamic parameters, serum creatinine, and creatinine clearance in 12 renal transplant patients converted from CsA to azathioprine (Aza) and in control patients (n = 9); base-line values (week 0) and relative changes from base-line. The last column denotes the p-value for the between-groups comparison of changes at 4 weeks.

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>P</th>
</tr>
</thead>
</table>
| Mean arterial pressure
(mmHg) | CsA —> Aza | 113 ± 11 | - 4 ± 8% | - 4 ± 7% | - 5 ± 7% | NS |
| | CsA | 111 ± 5 | - | - | - 2 ± 7% | |
| GFR
(ml/min/1.73 m²) | CsA —> Aza | 55 ± 18 | +15 ± 18% | +18 ± 26% | +18 ± 24% | 0.036 |
| | CsA | 61 ± 15 | - | - | - 2 ± 17% | |
| RPF
(ml/min/1.73 m²) | CsA —> Aza | 267 ± 117 | +27 ± 43% | +27 ± 35% | +21 ± 36% | NS |
| | CsA | 306 ± 92 | - | - | - 3 ± 18% | |
| RVR
(arbitrary units) | CsA —> Aza | 0.36 ± 0.22 | -18 ± 21% | -18 ± 22% | -12 ± 26% | NS |
| | CsA | 0.25 ± 0.12 | - | - | + 4 ± 30% | |
| Serum creatinine
(μmol/l) | CsA —> Aza | 125 ± 41 | - 7 ± 9% | -11 ± 10% | -13 ± 9% | 0.001 |
| | CsA | 116 ± 25 | - | - | + 4 ± 9% | |
| Creatinine clearance
(ml/min/1.73 m²) | CsA —> Aza | 70 ± 21 | +11 ± 23% | +16 ± 38% | +20 ± 44% | NS |
| | CsA | 79 ± 20 | - | - | - 3 ± 12% | |

*p <0.05, **p <0.01 for differences versus base-line values.
Table 2  Serum levels of potassium, bicarbonate, magnesium, and urate, and tubular handling of sodium in 12 renal transplant patients converted from CsA to azathioprine (Aza) and in control patients (n = 9); base-line values (week 0) and absolute changes from base-line. The last column denotes the p-value for the between-groups comparison of changes at 4 weeks.

<table>
<thead>
<tr>
<th>Weeks</th>
<th>P CsA → Aza vs CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Table 3  Tubular handling of sodium in 8 renal transplant patients who were converted from CsA to azathioprine and did not use nifedipine; base-line values (week 0) and absolute changes from base-line.

<table>
<thead>
<tr>
<th>Weeks</th>
<th>FE (%)</th>
<th>FPR (%)</th>
<th>FDR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.4 ± 0.8</td>
<td>65.9 ± 7.7</td>
<td>89.7 ± 2.2</td>
</tr>
<tr>
<td>1</td>
<td>+0.1 ± 0.9</td>
<td>-7.3 ± 8.0</td>
<td>+1.6 ± 2.1</td>
</tr>
<tr>
<td>2</td>
<td>-0.3 ± 1.4</td>
<td>-4.8 ± 6.9</td>
<td>+2.2 ± 4.0</td>
</tr>
<tr>
<td>4</td>
<td>-0.2 ± 1.0</td>
<td>-5.7 ± 10.5</td>
<td>+1.8 ± 3.2</td>
</tr>
</tbody>
</table>

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remaining 8 patients there was a slight decrease in FPR at one week after conversion, while a significant increase in FDR was lacking in this subgroup of patients. Meaningful comparisons with the control group were not possible since only two members of this group did not use nifedipine.

The relative change in serum creatinine showed a significant correlation with the relative change in GFR (at 1 week: r = -0.76, p <0.01; at 4 weeks: r = -0.57, p = 0.055). Although the improvement in renal function and the decrease of serum urate were of equal magnitude, there was no significant correlation between both changes. Likewise, the change in serum magnesium was not correlated with the change in either GFR or serum creatinine.

**Discussion**

This controlled study of the changes in renal function that occur after discontinuation of CsA demonstrates that these changes largely take place during the first week following cessation of the drug. At one week after conversion, GFR had improved with 15% and in the ensuing weeks only a minor, non-significant, further increase in GFR was observed. As expected from literature data, the increase in GFR was accompanied by a rise in RPF and a decrease in RVR [Curtis et al. 1986, Zietse et al. 1994]. Accordingly, our findings support the conclusion by others that renal vasoconstriction is involved in the reversible form of CsA-induced renal dysfunction [Conte et al. 1989, Sabbatini et al. 1993]. The fall in serum creatinine
lasted slightly longer than the rise in GFR, which may partly be due to the time needed to achieve a new steady state of the serum creatinine level after a change in creatinine clearance. The relevance of these findings is that in clinical practice as well as in investigational circumstances the outcome of CSa withdrawal with regard to renal function can already be judged reliably after two weeks. When the interval between cessation of CSa and the time of evaluation becomes longer, the chance increases that measurement of the effects of CSa withdrawal becomes disturbed by other factors. One of these confounding factors in renal transplant patients can be a change in renal function due to an acute rejection episode which sometimes occurs already in the first month after conversion from CSa to azathioprine [Hoitsma et al. 1987].

Generalization of the results may be limited by the fact that the study was carried out in CSa-treated patients with rather well functioning grafts. Some selection-bias may have occurred in this respect since it has been our policy to replace CSa by azathioprine prematurely in patients in whom poor graft function was suspected to be worsened further by CSa-related nephrotoxicity. In addition, the fluid load and the supine position of the patients may have raised the measured GFR to some extent.

In previous studies, a decrease in the fractional clearance of lithium ($\text{FE}_{\text{Li}}$) has been suggested to be a sensitive marker of CSa-induced renal dysfunction [Dieperink et al. 1987, Vincent et al. 1988, Propper et al. 1990]. At first sight, we were not able to confirm these findings as the fractional proximal sodium reabsorption (which was calculated by the formula $100 - \text{FE}_{\text{Na}}$) did not change after discontinuation of CSa. However bias appeared to be introduced by treatment with the calcium antagonist nifedipine in four patients. Use of nifedipine during CSa therapy was associated with higher levels of $\text{FE}_{\text{Na}}$ and $\text{FE}_{\text{Li}}$ which agrees with the known effects of this drug [Krussel et al. 1987, Wetzels et al. 1988]. Indeed, analysis of the data after exclusion of the four nifedipine using patients, revealed a decrease in the PPR$_{\text{Na}}$ (corresponding to an increase in $\text{FE}_{\text{Li}}$) at one week after conversion. The tendency of the fractional distal sodium reabsorption to increase may reflect a reversal of the CSa-induced hyporeninemic hypo-aldosteronism [Bantle et al. 1985]. The observed increase in serum bicarbonate as well as the decrease in serum potassium also fit with recovery from a hypo-aldosteronemic state.

Hypomagnesemia and hyperuricemia are well known side-effects of CSa. Nevertheless, we were surprised to find that the rise in serum magnesium as well as the fall in serum urate levels were the most consistent changes already occurring during the first week following conversion from CSa to azathioprine. The serum magnesium level rose in all patients and the urate concentration decreased in all but one patient in whom it remained constant. Thus, in our hands the magnesium and urate levels were the most sensitive markers of the acute renal effects of CSa. The mechanisms by which CSa changes the serum levels of magnesium and urate are not quite clear. Theoretically, hyperuricemia may result from a decrease in the filtered load of urate with impaired GFR, from an independent effect of CSa on tubular urate transport, or from both of these factors. The lack of correlation between the decrease in serum urate and the increase in the FPRN1, (corresponding to a decrease in the $\text{FE}_{\text{Li}}$, (corresponding to a decrease in GFR) is largely attained with rather well functioning grafts. However bias appeared to be introduced by treatment with the calcium antagonist nifedipine in four patients. Use of nifedipine during CSa therapy was associated with higher levels of $\text{FE}_{\text{Na}}$ and $\text{FE}_{\text{Li}}$ which agrees with the known effects of this drug [Krussel et al. 1987, Wetzels et al. 1988]. Indeed, analysis of the data after exclusion of the four nifedipine using patients, revealed a decrease in the PPR$_{\text{Na}}$ (corresponding to an increase in $\text{FE}_{\text{Li}}$) at one week after conversion. The tendency of the fractional distal sodium reabsorption to increase may reflect a reversal of the CSa-induced hyporeninemic hypo-aldosteronism [Bantle et al. 1985]. The observed increase in serum bicarbonate as well as the decrease in serum potassium also fit with recovery from a hypo-aldosteronemic state.

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