A positive effect of AII inhibitors on peritoneal membrane function in long-term PD patients

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Abstract

Background. Experimental studies showed that inhibition of AII effects attenuates the development of peritoneal membrane fibrosis and neoangiogenesis. The latter leads to an increase of peritoneal solute transport and ultrafiltration failure. The results of a single-centre study showed that use of ACEI/ARB can prevent the increase of small solute transport in long-term PD patients. Our aim was to investigate whether these results would also be present in a larger population and influence patient and technique survival in long-term PD.

Methods. We analysed data from 217 long-term CAPD patients, participating in the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD). Included patients underwent CAPD therapy for at least 2 years; 120 of them were treated with the ACE/AII inhibitors-ACEI/ARB group. The control group consisted of 87 patients who received none of the above drugs and 10 patients who had them for <25% of their time on PD.

Results. A significant difference in the time course of peritoneal transport was found between the two groups. The value of 24-h D/P creatinine was associated with the PD duration (P = 0.01) and its time course was influenced by use of ACEI/ARB (P = 0.05). We found no effect of ACEI/ARB on patient survival, but some benefit was found for the technique survival: in a multivariate model the hazard ratio for the group with the longest use of ACEI/ARB was 0.5 (CI 0.22–1.4), P = 0.19.

Conclusions. We conclude that AII inhibition prevents the increase in small solute transport in long-term PD. These drugs may also have some positive influence on PD technique survival.

Keywords: ACE inhibitors; angiotensin II receptor blockers; peritoneal dialysis; technique survival; transport

Introduction

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are used extensively in patients with renal diseases because of their beneficial effects on the cardiovascular system, their ability to reduce proteinuria and influence the time course of the decline in glomerular filtration rate (GFR) in patients with various forms of glomerulopathies [1,2]. The latter is likely due to the fact that angiotensin II (AII) has the properties of a growth factor [3]. That explains an ability of AII inhibitors to attenuate development of renal fibrosis [4], predominantly by suppressing the activity of transforming growth factor-β (TGF β) [5].

The fibrotic and diabetic form of vascular alterations that can be found in long-term peritoneal dialysis (PD) patients [6,7] are likely to be mediated by TGF β and vascular endothelial growth factor (VEGF) [8,9]. This has focused interest on the possibility of using ACEI/ARB to influence these membrane changes. In vitro studies using cultured mesothelial cells showed that AII mediates the upregulation of TGF β, induced by high glucose exposure [10]. Another study found that ACEI/ARB suppressed the production of VEGF [11]. Earlier experimental studies have shown that ACE inhibitors had a positive impact on the development of peritoneal membrane morphological alterations such as fibrosis and neoangiogenesis [12].

To our knowledge, there are no studies other than the ones done by our group, which focused on long-term effects of ACEI/ARB in humans, treated with PD. We reported previously about the effects of AII inhibitors on peritoneal membrane function in long-term PD patients in a single-centre study [13]. The major finding was a different time course of small solute transport during the first 3–4 years of PD treatment. Patients receiving ACEI/ARB showed a slight decrease of the mass transfer area coefficient (MTAC) of creatinine. This was different from the controls in which an increase with time of treatment was found. It suggested inhibition of peritoneal angiogenesis. Therefore, these findings were in accordance with the results of the animal studies.
Although detailed information on various aspects of peritoneal transport changes over time was obtained, it was impossible to analyse the effects of ACEI/ARB on the PD technique and patient survival due to the relatively small number of patients. For this purpose, and also for the confirmation of our previous results in a larger patient group, we studied the CAPD population of the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD). Being focused mostly on long-term effects of the drugs, we excluded cases with early dropouts and included only patients who had been treated with continuous ambulatory peritoneal dialysis (CAPD) for 2 years.

**Patients and methods**

**Patients**

For the current analyses, we have selected patients from the database of the NECOSAD. This is a large prospective multicentre cohort study that contains data of incident dialysis patients from 38 dialysis units in the Netherlands. To be included into the study, a patient needed to be at least 18 years old and should have started renal replacement therapy with either form of dialysis. Afterwards, patients are followed as long as dialysis treatment continues.

Our study’s inclusion criteria were as follows: patients had to start renal replacement therapy with CAPD and remain on it for at least 2 years with breaks in therapy for not more than 3 months. Besides, patients needed to follow the standard CAPD prescription with a minimum of 8 l and a maximum of 10 l of dialysis fluid per day with 4–5 exchanges. Out of the NECOSAD database, we selected all incident patients who had started renal replacement therapy with PD in the period between 1 January 1997 and June 2006 and remained on PD for the next 3 months. Six hundred seventeen patients were found, 500 of which stayed alive on PD for at least a year. Out of these 500 patients, 321 were treated with CAPD for at least 1 year, and the other 179 were excluded because they were treated with either automated or nightly intermittent PD. The following year, 104 CAPD patients had stopped their PD treatment due to transfer to haemodialysis (28), having received a kidney transplant (40), death (25) and other reasons (12). The other 217 patients remained on CAPD after 2 years of treatment and were included into the study.

**Data collection**

Demographical data, as well as data on comorbidity and primary kidney disease, were collected within 1 month prior to the start of dialysis treatment. During the follow-up, data on blood pressure, use of antihypertensive medications, residual renal function and 24-h D/P creatinine ratios were collected at 3 and 6 months after the start of dialysis. Afterwards, data were collected on a half-yearly basis.

Primary kidney disease was classified according to the codes of the European Dialysis and Transplant Association—European Renal Association Registry. Comorbidity was scored on the basis of Davies’ comorbidity index. Cardiovascular disease was recorded if one of the following conditions was present: angina pectoris, myocardial infarction, congestive heart failure class III–IV, peripheral vascular disease or cerebral–vascular accident.

Residual renal function was expressed as residual GFR (rGFR) and calculated as the mean of creatinine and urea clearance, corrected for body surface area (ml/min/1.73 m²).

Peritoneal transport characteristics could be assessed by the dialysis adequacy and transport test (DATT) [14]. In this test, the dialysate/plasma creatinine (D/P creatinine) is calculated from a 24-h dialysate collection. The DATT provides reliable results in CAPD patients, but not in those on automated peritoneal dialysis (APD) [15]. For this reason, the current analysis had to be restricted to the CAPD population. If the CAPD treatment with a standard regime was interrupted (e.g. number of exchanges/volume was raised/lowered) or the patient completely switched to APD, such D/P values were treated as missing. There were 38 patients from the ACEI/ARB group and 36 from controls who had switched to other PD regimens during the follow-up period. Such therapy changes could have been temporary or permanent. In total, we excluded up to 30% of D/P creatinine values, which ranged from 15 to 25% per check-up time point. The number of excluded values was not different between the groups.

The number of patients using icodextrin for the long dwell was documented at every time point, and also the mean glucose concentration of the dialysis solutions used was calculated. The use of ACEI/ARB was documented ‘yes’ or ‘no’ at every check-up time point (see above). In the case of when ‘yes’ was indicated, the patient was considered to have used the medication during the period, preceding the check-up. We expressed the use of ACEI/ARB as percentage of the patient’s follow-up period, because the latter varied from 2 to 4 years.

**Statistical analysis**

To compare patients’ baseline characteristics, we used standard descriptive statistics. Results are expressed as means and standard deviations as well as medians and ranges in the case of non-normal distribution. Reasons for PD dropout were explored with the chi-square test.

To analyse the time course of D/P creatinine in relation to exposure to the drugs, we used a generalized linear mixed model for repeated measures. The generalized linear mixed model method was applied to take into account the correlation between repeated measurements (DATT) within the same patient. The random effects mixed model with unstructured covariate matrix was applied to test the interactions between variables. The multivariate model contained 24-h D/P creatinine as a dependent variable and treatment group and the number of DATTs as independent variables. The independent variables were first analysed separately, and then with an interaction.

To investigate whether there is an effect of ACEI/ARB on the rate of decline of residual GFR, we performed a linear mixed model that is described above.

Statistical analyses of patients’ and PD technique survival were performed by the Cox proportional hazards model. In the analysis of patient survival, the event was
death during PD treatment period, while transplantation and other reasons for PD drop-out were censored observations. For the analysis of technique survival, the event was transfer to haemodialysis and censored observations were death, transplantations and loss to follow-up.

In both patient and technique survival models, adjustments were made for a number of possible confounding effects as well as for some differences in baseline characteristics between the groups. These included age, gender, diabetes, cardiovascular comorbidity and mean arterial blood pressure at the start of dialysis.

All statistical analyses were performed using SPSS statistical software, version 12.0 (SPSS Inc., Chicago, IL, USA). A P-value of 0.05 or less was considered significant.

Results

Patients and baseline characteristics

Two hundred and seventeen CAPD patients were included into the study. It appeared that 120 patients were treated with ACE/All inhibitors (ACEI/ARB) for at least 25% of their follow-up time, and 87 patients did not receive these drugs during the entire follow-up. Ten patients received the drugs for <25% of the follow-up period and used them mostly at the start of PD. We considered it as a minor use of the medications and added these patients to the controls in order to have the more equal groups regarding the number of patients. The control group consisted of the 87 patients without any ACEI/ARB treatment and the 10 patients who used them for <25% of time—97 patients in total.

Data on demography, primary kidney disease, comorbidity and other baseline characteristics are given in Table 1. Patients on the ACEI/ARB were younger and had a higher prevalence of cardiovascular disease. They also had a higher blood pressure and used more antihypertensive medications at the start of PD treatment.

To study the effect of duration of exposure to the drugs, the ACEI/ARB group was also divided into two subgroups—patients treated with the drugs for >75% of their follow-up time (first group [59 patients]) and those treated with ACEI/ARB from 25 to 75% of the follow-up [second group (61 patients)]. Controls remained the same. Demographical and baseline data of the three groups are not given separately, but the group with longest exposure to ACEI/ARB had the highest cardiovascular comorbidity. The percentage of glucose in the PD solutions used by the patients per every time point was not different among the groups. Also the number of patients who used icodextrin during the follow-up was similar (data not shown).

Peritoneal transport

The number of patients’ values of D/P creatinine per time point of measurement, included for the analyses, was not different between the groups. The analysis showed a significant influence of time (year of follow-up) on the D/P creatinine curves (P = 0.01) (Figure 1). It also showed a significantly different time course of D/P creatinine for the two study groups (Figure 1a), P = 0.05. The subanalysis of

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; GFR, glomerular filtration rate.

ACEI/ARB >75%

ACEI/ARB 25-75%

ACEI/ARB >75%

controls

ACEI/ARB 25-75%

ACEI/ARB >75%

controls

ACEI/ARB 25-75%

ACEI/ARB >75%

controls

ACEI/ARB 25-75%

ACEI/ARB >75%

controls

ACEI/ARB 25-75%

ACEI/ARB >75%

controls

ACEI/ARB 25-75%

ACEI/ARB >75%

controls

ACEI/ARB 25-75%

ACEI/ARB >75%

controls

ACEI/ARB 25-75%
the three groups showed that the group with the longest use of ACEI/ARB had the lowest D/P creatinine ratios during the follow-up, \( P = 0.1 \) (Figure 1b).

Mortality
The mean follow-up period was 3 years (range 2–8 years). Forty-eight patients died, seventy-eight received a kidney transplant and thirty-nine were transferred to haemodialysis. Fifty-two patients were lost to follow-up due to various reasons (refusal to participate, transfer to another centre, etc.) or still continuing PD treatment at the time of censoring. Table 2 presents the reasons for PD drop-out for the two groups separately. None of the differences was significant. Also, no effects were found in the analysis of the three groups (data not shown).

No effect on patient survival was found between the ACEI/ARB and control group. In the univariate Cox proportional hazard model, the relative risk of death (hazard ratio, HR) for the ACEI/ARB group was 1.03 [95% confidence interval (CI) 0.5–1.8]. After adjustment for age, sex, cardiovascular comorbidity, diabetes and mean arterial blood pressure at baseline, the HR was 1.1 (95% CI 0.6–2.2). In the analysis of the three groups, the relative risk of death for group 1 (ACEI/ARB >75%) was 0.9 (95% CI 0.4–2.1) and for group 2 (ACEI/ARB 25–75%) 1.2 (95% CI 0.6–2.7). Age and the presence of cardiovascular comorbidity were found to be significant predictors of death.

Technique survival
We found some positive effect of ACEI/ARB on PD technique survival, although statistical significance was not reached, \( P = 0.19 \) (Figure 2). Patients who received ACEI/ARB for the longest duration tended to have the best PD technique survival and controls did the worst (Table 3). No difference was found between the two groups in the reasons for transfer to HD.

Decline of residual GFR
We found no difference between the two groups with regard to the rate of decline of residual GFR (Figure 3).

Table 2. Reason for drop-out from PD (data given in exact numbers)

<table>
<thead>
<tr>
<th>Reason for dropout</th>
<th>ACEI/ARB</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer to HD</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Transplantation</td>
<td>48</td>
<td>30</td>
</tr>
<tr>
<td>Death</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Other(^a)</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Continuing PD(^b)</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; PD, peritoneal dialysis.

\(^a\)Includes loss to follow-up (transfer to another centre, refusal to participate by patient/or centre, etc.).

\(^b\)Continuing PD treatment after date of censoring.

None of the differences was significant.

Table 3. Unadjusted and adjusted hazard ratios for PD technique survival (results of three subgroups analysis)

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard ratio (95% CI)</th>
<th>Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB &gt;75% versus controls</td>
<td>0.65 (0.2–1.4)</td>
<td>–</td>
</tr>
<tr>
<td>ACEI/ARB 25–75% versus controls</td>
<td>0.77 (0.3–1.6)</td>
<td>Age, sex, initial mean arterial BP, diabetes, cardiovascular disease</td>
</tr>
<tr>
<td>ACEI/ARB &gt;75% versus controls</td>
<td>0.5 (0.22–1.4)</td>
<td>Age, sex, initial mean arterial BP, diabetes, cardiovascular disease</td>
</tr>
<tr>
<td>ACEI/ARB 25–75% versus controls</td>
<td>0.8 (0.3–1.9)</td>
<td>Age, sex, initial mean arterial BP, diabetes, cardiovascular disease</td>
</tr>
<tr>
<td>ACEI/ARB &gt;75% versus controls</td>
<td>0.64 (0.23–1.7)</td>
<td>Age, sex, initial mean arterial BP, diabetes, cardiovascular disease + baseline rGFR</td>
</tr>
<tr>
<td>ACEI/ARB 25–75% versus controls</td>
<td>0.75 (0.31–1.7)</td>
<td>Age, sex, initial mean arterial BP, diabetes, cardiovascular disease + baseline rGFR</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; rGFR, residual glomerular filtration rate.
Discussion

The results of the present study have shown that treatment with ACEI/ARB in CAPD patients may prevent or retard the increase in D/P creatinine that often occurs during long-term PD [16]. As D/P creatinine is dependent on the vascular peritoneal surface area, the data suggest less peritoneal angiogenesis than in those who did not receive ACEI/ARB. Our results are in line with those of a smaller single-centre analysis in a different patient population, using MTACs during a standardized peritoneal permeability analysis [13]. The suggestion of less neoangiogenesis during ACEI/ARB supports the findings in animal models [12]. These showed a beneficial effect on the number of peritoneal vessels and on the amount of fibrosis.

Protection of the peritoneal membrane has never been the reason for prescribing ACEI/ARB. The common indications were applied such as hypertension or heart failure. Two studies on a beneficial effect of ACEI/ARB on the time course of residual renal function in a selected population of incident PD patients have been published in 2003–2004 [17,18]. The inclusion of patients in our study ended in 2003. Therefore, preservation of rGFR is highly unlikely to have been a reason to prescribe ACEI/ARBs in our cohort. As such, the use of these drugs can be considered as a random process with regard to the peritoneal membrane and residual renal function preservation. However, a formal randomized controlled trial (RCT) with a sufficiently long follow-up period would be the approach to confirm or reject the hypothesis that AII inhibitors have a peritoneal protective effect. Yet, this may also be subject to a bias, at least in those countries where these drugs are available for everyone who needs them. In the case of exclusion of patients who have generally accepted indications for ACEI/ARB treatment, there is a risk to end up with a highly selected group of randomized patients. In such a situation, when an RCT is not possible to perform or may be inadequate, the results of a properly controlled observational cohort study can give valuable conclusive information [19,20].

The duration of PD for at least 2 years was required to be included in the present study. This is different from other studies performed in PD patients that were all short term and focused on the effects of ACEI/ARB on blood pressure and peritoneal clearances, as discussed in [13]. The results of these investigations on the peritoneal transport were inconclusive. The reason to restrict the study to patients having completed 2 years was our objective to study long-term peritoneal changes and the fact that these do not occur before 3–4 years on PD.

We also excluded patients who were not treated with a standard CAPD regimen. The reason for that is the use of the DATT. This parameter is influenced by the dialysis volume and by the dwell time. For instance, large volumes and short dwell times, as often used in APD, will give low values for 24-h D/P creatinine. Therefore, the volumes and the dwell times had to be standardized to some extent (see the Patients and methods section). We do not think that excluding the various forms of APD has influenced the results of our study, because no data are available suggesting that the time course of peritoneal transport would be different in CAPD and APD.

Our study enabled us to analyse patient and technique survival. For patient survival, it is important that some differences were present between the ACEI/ARB group and controls. Patients on ACEI/ARB were younger, had more cardiovascular comorbidity, higher blood pressure and a greater proportion of them used antihypertensives. This reflects the common indications for the prescription of these drugs. Taking these risk factors into account, one can presume that patients who received ACEI/ARB would have a higher mortality risk than the controls. However, both in the unadjusted and the adjusted analyses, neither a negative nor a positive effect on patient survival was found. It may be that the higher comorbidity counteracted a potentially positive effect of ACEI/ARB on patient survival.

Analysis of PD technique survival indicated some positive effect of ACEI/ARB, which was mainly present for the group who received the drugs for at least 75% of the follow-up. After correction for age, gender, diabetes, blood pressure and cardiovascular disease, the effect was even stronger. We found no influence of baseline rGFR. We also did not find any effect of the drugs on the rate of decline of rGFR which is different from the results of the earlier studies [17,18]. It should be noted, however, that both studies were RCTs with a highly selected patient population like a low cardiovascular comorbidity and a short follow-up. A favourable effect of ACEI/ARB on residual GFR might be different in a cohort with higher comorbidity and a long-follow-up.

It can be concluded that ACEI/ARB prevents the increase of small solute transport that often takes place in long-term PD. This is in line with some experimental study results and with our previous finding obtained in a single-centre study. Besides, the results of the current study also suggest that a membranoprotective effect of AII inhibitors may positively influence PD technique survival in long-term patients.


Conflict of interest statement. None declared.

References

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