Strategies to optimize renoprotective therapy in proteinuric renal patients
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Chapter 4

Altering the dosing time of trandolapril does not increase the antiproteinuric effect of ACE inhibition in non-diabetic kidney disease

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Background—Angiotensin-converting enzyme (ACE) inhibitors are drugs of first choice to reduce proteinuria in renal diseases, but the antiproteinuric response may vary highly. We previously observed a relative therapy resistance to blockade of the renin-angiotensin-aldosterone system (RAAS) during the night. Since higher residual proteinuria is associated with more rapid renal function loss, it is important to enhance the nocturnal antiproteinuric response. We therefore questioned whether altering the dosing time of the ACE inhibitor trandolapril could overcome the relative nocturnal therapy resistance.

Methods—Fourteen non-diabetic proteinuric patients on stable RAAS inhibition, with residual proteinuria of > 1 g/d were converted to trandolapril (4 mg) in the morning. Other antihypertensive medication was continued. After 6 weeks, patients were randomized to evening (4 mg) or BID (2 x 2 mg) dosing of trandolapril in a cross-over fashion (6 weeks each). During the last study period, patients again used trandolapril (4 mg) in the morning. Patients collected 2 x 24-h urine in day- and nighttime portions every 6-week period. Proteinuria and blood pressure were measured.

Results—Total residual proteinuria and blood pressure were equal during all periods. Daytime and nighttime proteinuria were also comparable during all periods. Blood pressure diurnal rhythm was similar during all periods. Evening and BID dosing did not affect total residual proteinuria, daytime or nighttime proteinuria. Sodium and protein intake were not significantly different among the different dosing regimens.

Conclusions—Altering the dosing time of the ACE inhibitor, trandolapril, does not increase the antiproteinuric response. Therefore, once daily dosing of the long-acting ACE inhibitor, trandolapril, at maximum dose results in its optimal antiproteinuric effect.

Intervention in the renin-angiotensin-aldosterone system (RAAS) with ACE inhibitors or angiotensin type 1 receptor (AT1) antagonists is the preferred antiproteinuric therapy for renal disease since these drugs reduce proteinuria beyond their blood pressure lowering effect (1,2). This specific property of RAAS inhibitors results in a reduced rate of renal function loss compared to non-RAAS antihypertensive treatment (3). Yet, in a given patient population, there is a large variability in antiproteinuric therapy response to ACE inhibitors (4). This is of clinical importance because the lower the residual proteinuria (presumably < 1 g/d) the better kidney function is preserved on the long term (5,6).

Proteinuria usually displays a circadian rhythm with maximum urinary protein excretion during the day (7), probably involving diurnal changes in blood pressure, renal haemodynamics (8,9), glomerular permeability (9) and tubular reabsorption. We previously observed a relative therapy resistance during the night to the antiproteinuric
action of a single morning dose of the ACE inhibitor trandolapril (10), despite comparable reduction of blood pressure during both daytime and nighttime. Consequently, nighttime protein excretion under ACE inhibitor therapy contributes relatively strongly to the residual proteinuria, and may thus represent an important target for optimization of the therapeutic response. As ACE inhibitors are routinely dosed in the morning, we questioned whether alternative timing of dosing may overcome nocturnal therapy resistance in non-diabetic patients with significant residual proteinuria during RAAS inhibition.

METHODS

Patients

This study was performed in accordance to the Declaration of Helsinki, approved by the local Medical Ethical Committee, and all patients gave their informed consent. Fourteen Caucasian, non-diabetic patients with chronic renal disease and residual proteinuria > 1 g/d on stable RAAS-inhibiting therapy were enrolled. Only patients with an age between 18 and 70 yrs, and a creatinine clearance (CLcr) ≥ 30 mL/min/1.73m² were included. Exclusion criteria were uncontrolled hypertension (systolic blood pressure (SBP) > 180 mmHg or diastolic blood pressure (DBP) > 100 mmHg) during the run-in period, a history of myocardial infarction, unstable angina, heart failure, coronary by-pass surgery or cerebrovascular accident during the past 6 months, frequent use of non-steroidal anti-inflammatory drugs (> 2 doses weekly), use of immunosuppressants, high rate of renal function loss (decline in CLcr > 6 mL/min/year during the previous year), serum potassium ≥ 6 mmol/L, intolerance or contra-indication for the use of ACE

Table 1. Baseline patient characteristics. Data are expressed as median (95% CI)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>7/7</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>48 (28-62)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.1 (22.8-35.0)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>3 FGS, 2 MGP, 3 IgA, 3 other, 3 no/NCBx</td>
</tr>
<tr>
<td>Residual proteinuria (g/24h)</td>
<td>3.0 (1.3-5.7)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>126 (118-148)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 (67-88)</td>
</tr>
<tr>
<td>CLcr (mL/min)</td>
<td>87.5 (38.1-99.3)</td>
</tr>
<tr>
<td>Antihypertensive medication (number of users)</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>12</td>
</tr>
<tr>
<td>AT1 antagonists</td>
<td>6</td>
</tr>
<tr>
<td>Dual RAAS blockade</td>
<td>4</td>
</tr>
<tr>
<td>Diuretics</td>
<td>9</td>
</tr>
<tr>
<td>β-blockers</td>
<td>4</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>4</td>
</tr>
</tbody>
</table>

BMI, body mass index. FGS, focal glomerulosclerosis. MGP, membranous glomerulopathy. IgA, IgA nephropathy. No/NCBx, no or non-conclusive biopsy.
inhibitors and inability to understand the patient information. The characteristics of the 14 patients enrolled in this study are shown in table 1.

**Study protocol**

This prospective, randomized, open-label, cross-over study was performed on an ambulatory basis (figure 1). Patients visited the outpatient clinic with 6 weeks intervals. All RAAS inhibition was stopped and converted to trandolapril 4 mg in the morning after patients gave informed consent. We chose not to use a washout period without any RAAS inhibition, because this may result in a deterioration of renal function. More importantly, a washout period is not necessary to answer the study question whether alteration of the dosing time of an ACE inhibitor can amplify its antiproteinuric efficacy. Other antihypertensive medication was continued during the study, but the dosage of these drugs was not changed during the complete protocol. Patients were instructed to take their non-study medication on regular fixed times of the day, preferably in the morning. The study consisted of 4 6-week periods. As previous studies demonstrated that proteinuria stabilizes 4 weeks after the start of RAAS inhibition (1,2), we chose to use 6-week treatment periods to rule out the influence of carry-over effects. After an initial run-in period of 6 weeks of morning dosing of trandolapril (4 mg), the patients were randomized to periods of evening dosing (4 mg at 10.00 p.m.) and BID (2 x 2 mg at 8.00 a.m. and 8.00 p.m.) in a cross-over fashion (6 weeks each). To control for time influences, all patients were treated with a morning dose of trandolapril (4 mg at 8.00 a.m.) during the final 6-week period of the study.

**Measurements**

The patients visited the outpatient clinic in the morning after an overnight fast, without taking any blood pressure affecting medication. A blood sample was drawn and trough blood pressure was measured in a semisupine position with a Dinamap apparatus for 15 min with a 1 min interval. The mean of the last 5 measurements was taken for analysis. In addition, 9 patients underwent a 24-h blood pressure measurement in each study period at 15 min intervals during the day and 30 min intervals during the night using an

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**Figure 1.**

Study design: dosing times of trandolapril. Half of the patients (n = 7) were randomly allocated to the upper arm and the other half (n = 7) to the lower arm.
ambulatory blood pressure meter (Spacelabs model 90207). At the end of each 6-week period, patients collected 2 x 24 h urine in daytime and nighttime portions. The daytime period was from 8.00 a.m. until 10.00 p.m., whereas the nighttime period was from 10.00 p.m. until 8.00 a.m. Patients were instructed to adhere to a mild sodium restricted diet (< 100 mmol Na/day) throughout the study. Proteinuria was measured using the benzethonium chloride method. Serum and urinary creatinine were analyzed by Jaffé reaction. Urinary sodium was measured with an ion-selective electrode and urinary urea was measured enzymatically using urease.

**Statistical analysis**

Data are expressed as median with 95% confidence interval. Based on previous clinical experience, a 25% reduction of proteinuria, after shifting from morning to evening or BID dosing, was considered clinically relevant. For a desired power of 0.8 and a two-sided alpha of 0.05, a total of at least 10 patients was needed to detect such a reduction of proteinuria. Missing value analysis was performed for the 24-h blood pressure measurements using expectation maximization. Because of the small number of patients data from the 4 study periods were analyzed with a non-parametric Friedman’s ANOVA for paired observations with correction for multiple comparisons. Wilcoxon signed rank test was used for differences between daytime and nighttime data. A p-value < 0.05 was considered statistically significant.

**RESULTS**

The median residual proteinuria of patients at recruitment was 3.0 (1.3-5.7) g/24h on their pre-study RAAS-inhibiting medication (table 1). The conversion to morning dosing of trandolapril 4 mg resulted in a similar residual proteinuria of 3.0 (1.9-4.2) g/24h after 6 weeks. Changing of dosing in the subsequent 6-week periods to evening (4 mg) and BID (2 x 2 mg) dosing did not influence residual proteinuria significantly (figure 2A). Sodium and protein intake were not significantly different among the different dosing regimens, although the sodium intake was higher than prescribed. Urinary creatinine excretion remained stable throughout the study (table 2).

Subsequently, we examined whether changing of the dosing time affected the amount of residual proteinuria during daytime and nighttime (figure 2B). Both daytime and nighttime urinary protein excretion were not significantly different among the 4 dosing periods. Three patients showed a favourable response of > 25% reduction in residual proteinuria on switching from morning to evening dosing. Five patients had such a response on switching from morning to BID dosing. These numbers are too small to identify specific patient characteristics which determine a favourable response to a switch in dosing time.
Both trough SBP and DBP were equal during all therapy regimen periods (table 2). Ambulatory measurement showed a significant lower SBP and DBP during the night compared to daytime (p < 0.05), without any significant differences between the dosing regimes.

**DISCUSSION**

In this study, we found no effect of altering the dosing time of the long-acting ACE inhibitor trandolapril on residual proteinuria in non-diabetic renal patients. We observed an equal urinary protein excretion rate during daytime and nighttime in non-diabetic patients treated with a single morning dose of trandolapril. Changing from morning dosing to BID or evening dosing did not result in greater reduction of proteinuria during nighttime compared to daytime. As in untreated proteinuric patients proteinuria during daytime exceeds nocturnal proteinuria (10), our data also suggest a relative therapy

**Table 2.** Proteinuria, blood pressure and urinary urea, sodium and creatinine excretion during the 4 treatment periods (median and 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Morning</th>
<th>BID</th>
<th>Evening</th>
<th>Morning</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>130 (112-149)</td>
<td>128 (110-145)</td>
<td>134 (107-154)</td>
<td>130 (109-146)</td>
</tr>
<tr>
<td>daytime (mmHg)</td>
<td>124 (117-137)</td>
<td>121 (117-138)</td>
<td>128 (120-139)</td>
<td>124 (109-130)</td>
</tr>
<tr>
<td>nighttime (mmHg)</td>
<td>109 (105-119)*</td>
<td>107 (102-117)*</td>
<td>110 (105-115)*</td>
<td>111 (91-120)*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79 (66-84)</td>
<td>74 (64-87)</td>
<td>79 (65-85)</td>
<td>80 (66-85)</td>
</tr>
<tr>
<td>daytime (mmHg)</td>
<td>81 (74-85)</td>
<td>82 (76-83)</td>
<td>83 (72-89)</td>
<td>83 (72-86)</td>
</tr>
<tr>
<td>nighttime (mmHg)</td>
<td>69 (60-76)*</td>
<td>64 (55-71)*</td>
<td>68 (55-72)*</td>
<td>68 (54-78)*</td>
</tr>
<tr>
<td>U_urea (mmol/24h)</td>
<td>334 (263-477)</td>
<td>316 (267-450)</td>
<td>297 (249-438)</td>
<td>312 (253-444)</td>
</tr>
<tr>
<td>U_Na+ (mmol/24h)</td>
<td>175 (126-248)</td>
<td>141 (119-191)</td>
<td>174 (144-216)</td>
<td>156 (99-203)</td>
</tr>
<tr>
<td>U_Cr (mmol/24h)</td>
<td>13.7 (12.1-18.1)</td>
<td>12.2 (10.7-17.6)</td>
<td>12.2 (11.0-17.1)</td>
<td>11.5 (10.8-15.8)</td>
</tr>
</tbody>
</table>

U_urea, urinary urea excretion. U_Na+, urinary sodium excretion. U_Cr, urinary creatinine excretion. * p < 0.05 nighttime vs. daytime
resistance to ACE inhibitors during nighttime.

What could explain the relative therapeutic resistance of nocturnal proteinuria to ACE inhibition? A possible explanation may be offered by the physiological diurnal variation in the activity of the RAAS, having its peak renin and aldosterone activity early in the morning and the lowest activity during the evening (11), and ACE-activity peaking in the afternoon (12). Optimal efficacy of RAAS blockade may be dependent on activation of the system, as shown by an augmentation of the antiproteinuric response to ACE inhibitors by diuretics and low salt diet (13). Consequently, the lower nocturnal activity of RAAS may impair its therapeutic efficacy. Such a proposition is supported by the observation that blockade of the RAAS on another level by the renin inhibitor, remikiren (10), and dual RAAS inhibition with an ACE inhibitor and an AT1 antagonist (14) were also less effective in reducing nighttime proteinuria. Therefore, augmentation of the nighttime RAAS activity and the application of non-RAAS inhibiting antiproteinuric strategies may be more effective in reducing nighttime proteinuria.

Could the choice for trandolapril in our study have influenced our results? Trandolapril is a long-acting ACE inhibitor. The effective half-life of its active metabolite, trandolaprilat, is approximately 15-23h (15,16), due to its lipophilicity and saturable binding to ACE. We chose to use trandolapril at a dose of 4 mg per day, since with this drug and dose the optimal antiproteinuric effect is achieved (17). In spite of using an optimal antiproteinuric dose of a long-acting ACE inhibitor, we previously observed nocturnal therapy resistance to its antiproteinuric effect when the drug was administered in the morning (10). Trandolapril is claimed to inhibit the RAAS for 24 h by once daily dosing, supported by effective blood pressure reduction for 24 hours (10,18). Indeed, in our study no differences in SBP or DBP were observed during different dosing regimens. It should be noted that ACE inhibition in specific compartments (e.g. kidney tissue) may not last for 24 hours and antiproteinuric responses might therefore dissociate from systemic haemodynamic responses (1). The effect of changing the dosing time of RAAS blockade at the antiproteinuric efficacy in renal patients has not been previously studied. Only preliminary data are available from a study in Japanese proteinuric patients comparing morning dosing, evening dosing, and TID dosing of 3 mg of trandolapril (19). The antiproteinuric effect of trandolapril was most prominent during evening dosing, while TID dosing resulted in variable responses. Besides the differences in study design, a difference in genetic background of the patients or the use of a smaller dose may be an explanation for this difference with our results.

We conclude that altering the dosing time of the ACE inhibitor, trandolapril, is not an effective strategy to further reduce residual proteinuria. For clinical purposes, this means that once daily dosing of the long-acting ACE inhibitor trandolapril, at maximum
EFFECT OF DOSING TIME OF TRANDOLAPRIL ON PROTEINURIA

dose on an arbitrary time, results in its optimal antiproteinuric effect. Further research should be directed at other interventions which could further reduce residual proteinuria by ACE inhibitors in non-diabetic renal disease.

REFERENCES

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