Selective cyclooxygenase-2 (COX-2) inhibition reduces proteinuria in renal patients

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Abstract

Background. Renoprotection is predicted by the antiproteinuric efficacy of a pharmacological agent. Non-steroidal anti-inflammatory drugs (NSAIDs) interfering non-selectively in the prostaglandin system have strong antiproteinuric potency without reduction of systemic blood pressure. The effect of the selective COX-2 inhibitor rofecoxib in proteinuric patients is unknown, granted recently reported detrimental effects in non-renal patients. Short-term effects of rofecoxib on proteinuria and blood pressure as compared to NSAID and RAAS blockade were studied.

Methods. Sixteen stable patients [mean proteinuria 4.4 g/day; MAP 103 mmHg] were included after a wash-out period. Hydrochlorothiazide 12.5 mg QD was given throughout. Additional blood pressure control was ensured by non-RAAS blocking antihypertensive agents. Patients received rofecoxib 25 mg QD, 50 mg QD and indomethacin 75 mg BID in randomized order for 4 weeks. Thereafter, a subset of the included patients (n = 11) received lisinopril 40 mg QD for 6 weeks preceded by a wash-out period.

Results. Rofecoxib exerted a dose-dependent antiproteinuric effect. As compared to rofecoxib 25 and 50 mg, indomethacin was more effective [–19, –28 versus –49% (n = 16; P < 0.05)]. As compared to rofecoxib 50 mg, lisinopril was more effective [–21 versus –51% (n = 11; P < 0.05)]. No significant blood pressure changes were observed after rofecoxib and indomethacin, whereas lisinopril had a significant antihypertensive effect.

Conclusion. Selective COX-2 inhibition reduces proteinuria without reduction of systemic blood pressure, pointing towards a specific renal effect, and may serve as a novel non-hypotensive adjunct antiproteinuric treatment.

Keywords: chronic renal failure; COX-2 inhibition; NSAID; proteinuria; RAAS blockade

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Introduction

The reduction of blood pressure and proteinuria are the cornerstones of long-term renoprotection [1]. After the onset of treatment, the amount of residual proteinuria is the main predictor of subsequent renal function loss [2,3]. The reduction in blood pressure is generally associated with the reduction in proteinuria. As RAAS blockade exerts an antiproteinuric effect on top of the reduction of blood pressure, RAAS blockade is the therapy of choice for antiproteinuric intervention. To stop progressive renal function loss, the target for proteinuria is <1 g/day [4]. However, this target is not always reached as adverse effects, such as hypotension, limit the use of maximal blockade of the RAAS for titration of proteinuria towards the target [5]. Moreover, very low systolic blood pressure values (<110 mmHg) may negatively influence the long-term renal outcome [6]. Therefore, exploration of non-hypotensive strategies that lower proteinuria may expand the therapeutic arsenal.

Before the era of RAAS blockade, non-steroidal anti-inflammatory drugs (NSAIDs) have demonstrated to be highly effective to reduce proteinuria, in particular, when volume excess was corrected by sodium restriction and diuretics [7]. Antiproteinuric treatment with NSAID indomethacin seems to retard progression of renal function loss, as demonstrated in two independent retrospective studies [8,9]. The need for high doses and the related high frequency of side effects hampered further development of this drug class for renoprotection [10]. In fact, NSAIDs are mostly known for their adverse effects on the kidney [11]. Traditional NSAIDs exert their effects by blocking the production of prostaglandins, which are modulators of vascular tone, glomerular filtration, salt and water homeostasis and renin-secretion in the kidney [12,13,14]. In particular, the degree of prostaglandin E2 (PGE2) inhibition was associated with the antiproteinuric effect [15,16]. PGE2 is mainly derived from cyclooxygenase-2 (COX-2) that is up-regulated and newly expressed in renal tissue in response to renal disease [14], indicating that the degree of COX-2 inhibition may account for the renoprotective effect in proteinuric patients. The analgesic effects of NSAIDs, that inhibit the two isoforms of COX, COX-1 and COX-2,
are commonly attributed to inhibitory effects on COX-2, whereas their COX-1-inhibiting effects are associated with adverse effects on the gastrointestinal and central nervous system [13].

Selective COX-2 inhibitors comprise a class of drugs with reduced gastrointestinal complications. Recently, selective COX-2 inhibition has been related to detrimental effects on cardiac risk in non-renal patients [17,18]. In preclinical renal conditions, however, the effects of COX-2 inhibition may be beneficial. In non-diabetic and diabetic experimental renal disease, selective COX-2 inhibition reduced proteinuria and retarded the progression of glomerular injury [14]. In humans, little is known about the effects of selective COX-2 inhibition in chronic renal disease. The primary purpose of the present open-label study was to investigate the effect of the COX-2 inhibitor rofecoxib in two different doses on proteinuria, blood pressure and renal function in proteinuric patients, including a comparison with the traditional NSAID indomethacin. The secondary purpose of this study was to compare the effects of selective COX-2 inhibition with RAAS blockade, i.e. the ACE inhibitor lisinopril at maximal recommended dose.

**Materials and methods**

**Patients and protocol**

The study was approved by the local medical ethics committee, and all participants provided written informed consent. Patients with stable proteinuric nephropathy of glomerular origin or overtly diabetic nephropathy were selected from our renal outpatient department. Eligibility for participation in the study was considered after a run-in period (at least 6 weeks). In this period, patients refrained from RAAS blocking agents. Hydrochlorothiazide 12.5 mg QD was started and patients were instructed to adhere to a restricted sodium intake (<100 mmol/day) and standardized protein intake (1 g/kg body weight/day). Patients had to fulfil the following inclusion criteria after run-in: proteinuria ≥2 g/day, diastolic blood pressure <90 mmHg, creatinine clearance ≥30 mL/min and age between 18 and 70 years. During the run-in period, the addition of amlodipine (maximal daily dose 10 mg) or doxazosine (maximal dose 8 mg/day) was allowed for blood pressure control. These drugs were kept stable during the rest of the study. Patients with proteinuria due to a non-primary renal disorder other than diabetic nephropathy, as well as patients with systemic diseases and recent cardiovascular events (<6 months) were excluded. None of the participants received any immunosuppressive treatment previously (<6 months) or during the study. The study was performed before rofecoxib (VIOXX®, Merck & Co., Inc., Whitehouse Station, NJ, USA) was withdrawn from the market in response to the preliminary results of the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial [17]. Patients were treated according to a prospective open-label study protocol consisting of two parts. In the first part (protocol A), patients were treated with rofecoxib 25 mg QD, rofecoxib 50 mg QD and indomethacin 75 mg BID (retard formula; Indocid® Merck & Co., Inc., Whitehouse Station, NJ, USA) in random order, each preceded by a baseline period without the study medication. Indomethacin at the dose of 75 mg BID was chosen as the comparator since this dose had showed maximal antiproteinuric efficacy in previous studies as compared to other maximally dosed traditional NSAIDs [15]. Each period lasted 4 weeks. In the second part (protocol B), for direct comparison with the current treatment standards with proven renoprotective action, i.e. RAAS blockade, patients were also treated for 6 weeks with lisinopril at maximal recommended dose (40 mg QD) preceded by a 6-week wash-out period directly after protocol A. The treatment periods were 6 weeks, as previous studies have shown that within this period the maximal established antiproteinuric effect of RAAS blockade can be expected [19]. A pre-planned treatment period with the combination of rofecoxib on top of lisinopril could not be performed due to the withdrawal of rofecoxib.

**Measurements**

At the end of the run-in period and each study period, patients visited the hospital after an overnight fast. Blood was sampled, 24-h urine was collected and blood pressure was measured by an automatic device (Dinamap®, GE Healthcare, Waukesha, WI, USA). The mean arterial blood pressure (MAP) was calculated as 2/3 × diastolic blood pressure + 1/3 × systolic blood pressure. The mean value of four readings after 15 min was used for analysis. Urinary protein was determined with the pyrogallol red-molybdate method. Serum creatinine, albumin and lipids were determined using an automated multi-analyser (MEGA®, Merck, Darmstadt, Germany).

**Statistical analysis**

Results are expressed as mean and standard error (SE). Baseline data were obtained after the first run-in. The Student t-test was used for comparisons at baseline. Drug effects in all periods were evaluated by one-way ANOVA. In case of significance, post hoc Duncan correction was used for multiple comparisons. Correlation coefficients of treatment effects within patients were calculated using Pearson correlation. A P-value <0.05 was considered significant.

**Results**

**Patient characteristics**

Sixteen patients (11 males and 5 females) with mean (range) age of 55 (39–70) years were included. Of these patients, 9 patients suffered from non-diabetic nephropathy [including membranous glomerulopathy (3), primary focal segmental glomerular sclerosis (2), IgA nephropathy (2) and non-conclusive diagnosis (2)] and 7 from (type 2) diabetic nephropathy. After protocol A, a subset of patients comprising 11 of 16 patients were included for protocol B. Not all patients completed the protocol B due to preliminary withdrawal of the study drug rofecoxib (four patients), and one patient left the study due to personal circumstances. Baseline characteristics at the end of the run-in period are given in Table 1.
Table 1. Baseline characteristics at the end of run-in

<table>
<thead>
<tr>
<th></th>
<th>Protocol A</th>
<th>NDN (n = 9)</th>
<th>DN (n = 7)</th>
<th>Protocol B (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 (3)</td>
<td>59 (3)</td>
<td>52 (4)</td>
<td>55 (3)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>65%</td>
<td>50%</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>7</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>92 (4)</td>
<td>88 (6)</td>
<td>96 (6)</td>
<td>93 (5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31 (1)</td>
<td>28 (1)</td>
<td>34 (2)</td>
<td>30 (1)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>146 (4)</td>
<td>138 (5)</td>
<td>156 (6)*</td>
<td>146 (6)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>81 (2)</td>
<td>82 (3)</td>
<td>79 (3)</td>
<td>84 (2)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>4.4 (1.0)</td>
<td>5.8 (1.5)</td>
<td>2.7 (1.0)</td>
<td>5.6 (1.3)</td>
</tr>
<tr>
<td>Serum creatinine (g/L)</td>
<td>35 (1)</td>
<td>35 (1)</td>
<td>36 (1)</td>
<td>35 (1)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>93 (11)</td>
<td>89 (14)</td>
<td>98 (20)</td>
<td>79 (11)</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>35 (1)</td>
<td>35 (1)</td>
<td>36 (1)</td>
<td>35 (1)</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>3.6 (0.1)</td>
<td>3.8 (0.1)</td>
<td>3.6 (0.1)</td>
<td>3.9 (0.1)</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/L)</td>
<td>3.8 (0.5)</td>
<td>4.1 (0.8)</td>
<td>3.3 (0.6)</td>
<td>4.3 (0.7)</td>
</tr>
<tr>
<td>Renal function expressed as mean creatinine clearance (mL/min)</td>
<td>118 (4)</td>
<td>124 (5)</td>
<td>130 (3)</td>
<td>118 (4)</td>
</tr>
</tbody>
</table>

NA: not analyzed; NDN: non-diabetic nephropathy; DN: diabetic nephropathy.
*P < 0.05, non-diabetic versus diabetic nephropathy.
§subset of patients from protocol A.

Protocol A: Effects of rofecoxib as compared to indomethacin

In Table 2 and Figure 1, the results in the 16 proteinuric patients are summarized. Mean (SE) of treatment proteinuria was 4.8 (1.1) g/day. After treatment with rofecoxib 25 mg and 50 mg QD, mean proteinuria was significantly reduced by 18.6 (5.9)% and 27.7 (7.5)%, respectively (P < 0.05). The largest antiproteinuric response was observed after treatment with indomethacin 75 mg BID [48.9 (5.4)% (P < 0.05 versus baseline; P < 0.05 versus rofecoxib)]. Both diabetic and non-diabetic proteinuric patients showed similar antiproteinuric responses after different treatments, also after correction for 24-h urinary creatinine excretion.

MAP was 103 (2) mmHg. After rofecoxib 25 mg, MAP did not change significantly [103 (3) mmHg (0.4 (2.6)%)].

Dose titration with rofecoxib to 50 mg led to a borderline significant rise of MAP to 108 (2) mmHg [6.2 (3.0)% (P = 0.076)]. After indomethacin, MAP changed non-significantly to 104 (2) mmHg [0.9 (1.9)%]. When analysing diabetic and non-diabetic patients separately, a significant increase of MAP was only present in non-diabetic patients, but not in diabetic patients (Figure 1). Body weight was significantly increased at the end of all active treatments. Separate analysis showed that changes in non-diabetic patients accounted for the significant differences in body weight, since body weight did not alter significantly in diabetic patients (data not shown).

Renal function expressed as mean creatinine clearance was non-significantly decreased after rofecoxib 25 mg and 50 mg. After indomethacin, creatinine clearance decreased significantly (P < 0.05). Mean serum creatinine was not significantly increased after rofecoxib 25 mg. After rofecoxib 50 mg and indomethacin, serum creatinine was significantly increased (P < 0.05). To study the antiproteinuric efficacy related to changes in creatinine clearance during all treatments, the proteinuria-to-creatinine clearance ratio (i.e. fractional protein excretion) was calculated. After rofecoxib 25 mg and 50 mg, the ratio was significantly lowered as compared to baseline. The ratio was lowest after indomethacin treatment (P < 0.05 versus baseline; P < 0.05 versus rofecoxib).

Next to changes in serum creatinine, serum potassium increased significantly after rofecoxib 25 and 50 mg and indomethacin (P < 0.05). Indomethacin led to a significantly larger increase compared to rofecoxib 25 mg. In all patients, serum potassium was within the (normal) range of 3.5–4.5 mmol/L during all treatments of protocol A.

Protocol B: Effects of rofecoxib as compared to lisinopril

In Table 3 and Figure 2, the effects of treatment with rofecoxib 50 mg QD, indomethacin 75 mg BID and lisinopril 40 mg QD are summarized for the 11 patients that entered protocol B. The antiproteinuric response after lisinopril was greater than after rofecoxib 51.4 (9.6) versus 21.3 (7.4)% reduction (P < 0.05), but not different from indomethacin 44.6 (6.5)% reduction.

Lisinopril led to a significant reduction in systolic and diastolic blood pressure (P < 0.05), whereas no significant

The results of protocol A summarized

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1</th>
<th>Rofecoxib (25 mg)</th>
<th>Baseline 2</th>
<th>Rofecoxib (50 mg)</th>
<th>Baseline 3</th>
<th>Indomethacin (150 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria (g/day)</td>
<td>4.8 (1.1)</td>
<td>3.8 (0.8)*</td>
<td>4.5 (1.1)</td>
<td>3.7 (0.8)*</td>
<td>5.2 (1.3)</td>
<td>2.8 (0.9)*</td>
</tr>
<tr>
<td>Proteinuria/creatinine (mg/mg)</td>
<td>3.1 (0.6)</td>
<td>2.4 (0.5)*</td>
<td>2.9 (0.7)</td>
<td>2.3 (0.5)*</td>
<td>3.3 (0.8)</td>
<td>1.8 (0.5)*</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>147 (5)</td>
<td>147 (6)</td>
<td>146 (5)</td>
<td>155 (6)</td>
<td>143 (6)</td>
<td>150 (5)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>81 (2)</td>
<td>82 (3)</td>
<td>81 (2)</td>
<td>84 (3)</td>
<td>80 (2)</td>
<td>81 (2)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>91 (5)</td>
<td>93 (5)*</td>
<td>91 (5)</td>
<td>92 (5)*</td>
<td>90 (5)</td>
<td>92 (5)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>133 (17)</td>
<td>142 (19)</td>
<td>134 (19)</td>
<td>157 (21)*</td>
<td>144 (25)</td>
<td>155 (22)*</td>
</tr>
<tr>
<td>Serum creatinine (g/L)</td>
<td>3.6 (0.1)</td>
<td>3.8 (0.1)*</td>
<td>3.6 (0.1)</td>
<td>3.9 (0.1)*</td>
<td>3.6 (0.1)</td>
<td>4.0 (0.1)*</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>87 (12)</td>
<td>84 (12)</td>
<td>88 (13)</td>
<td>81 (15)</td>
<td>85 (13)</td>
<td>73 (11)*</td>
</tr>
<tr>
<td>Urinary sodium (mmol/day)</td>
<td>160 (21)</td>
<td>147 (20)</td>
<td>160 (21)</td>
<td>163 (17)</td>
<td>173 (18)</td>
<td>129 (15)*</td>
</tr>
<tr>
<td>Proteinuria/creatinine clearance (g/mL/min)</td>
<td>8.0 (2.4)</td>
<td>6.3 (1.7)*</td>
<td>7.9 (2.6)</td>
<td>7.0 (2.6)*</td>
<td>9.6 (3.9)</td>
<td>5.6 (2.0)*</td>
</tr>
</tbody>
</table>

*P < 0.05 versus baseline 1.
†P < 0.05 versus rofecoxib 25 mg.
‡P < 0.05 versus rofecoxib 50 mg.
§P < 0.05 versus baseline 3.

Table 2. Results of protocol A summarized
Fig. 1. Percentage change [mean (SE)] of proteinuria and blood pressure in 16 proteinuric patients from protocol A (table shows results of 9 non-diabetic and 7 diabetic patients separately analysed) after 4-week treatment with rofecoxib 25 mg QD, rofecoxib 50 mg QD and indomethacin 75 mg BID, respectively. *P < 0.05 versus baseline; †P < 0.05 versus rofecoxib 25 mg; ‡P < 0.05 versus rofecoxib 50 mg.

Table 3. Results of protocol B summarized

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Rofecoxib (50 mg)</th>
<th>Indomethacin (150 mg)</th>
<th>Lisinopril (40 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria (g/day)</td>
<td>5.8 (1.3)</td>
<td>4.1 (0.9)*</td>
<td>3.5 (1.2)*</td>
<td>2.8 (0.8)*</td>
</tr>
<tr>
<td>Proteinuria/creatinine (mg/mg)</td>
<td>3.6 (0.8)</td>
<td>2.6 (0.5)*</td>
<td>2.2 (0.7)*</td>
<td>1.8 (0.5)*</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>147 (6)</td>
<td>151 (5)</td>
<td>148 (6)</td>
<td>128 (7)*</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>82 (3)</td>
<td>84 (3)</td>
<td>81 (3)</td>
<td>70 (2)*</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>93 (5)</td>
<td>94 (5)</td>
<td>94 (5)</td>
<td>92 (5)*</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>78 (11)</td>
<td>77 (15)</td>
<td>64 (10)</td>
<td>64 (9)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>151 (22)</td>
<td>160 (25)</td>
<td>177 (27)*</td>
<td>186 (32)*†</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>3.5 (0.1)</td>
<td>3.8 (0.2)</td>
<td>4.0 (0.1)*</td>
<td>4.6 (0.2)*†</td>
</tr>
<tr>
<td>Urinary sodium (mmol/day)</td>
<td>139 (15)</td>
<td>163 (12)</td>
<td>114 (19)</td>
<td>165 (21)</td>
</tr>
<tr>
<td>Proteinuria/creatinine clearance (g/mL/min)</td>
<td>10.1 (3.2)</td>
<td>8.0 (3.3)</td>
<td>7.3 (2.7)*</td>
<td>5.7 (1.9)*</td>
</tr>
</tbody>
</table>

*P < 0.05 versus baseline.  †P < 0.05 versus rofecoxib 50 mg.  ‡P < 0.05 versus indomethacin 150 mg.

effect on systolic or diastolic blood pressure was observed after rofecoxib or indomethacin.

After lisinopril and indomethacin treatment, serum creatinine and potassium increased significantly, but not after rofecoxib. Moreover, creatinine clearance showed a non-significant trend to decrease in response to lisinopril and indomethacin. The fractional protein excretion measured as the proteinuria-to-creatinine clearance ratio was lowest after lisinopril treatment and differed significantly from rofecoxib (P < 0.05).

Individual responses

To investigate whether individual patients with a poor antiproteinuric responsiveness to ACE inhibitor therapy could benefit from a switch to rofecoxib, individual responses
Fig. 2. Percentage change [mean (SE)] of proteinuria and blood pressure in 11 proteinuric patients from protocol B (table shows results of 7 non-diabetic and 4 diabetic patients separately analysed), after 4-week treatment with rofecoxib 50 mg QD and indomethacin 75 mg BID and after 6-week treatment of lisinopril 40 mg QD, respectively. *P < 0.05 versus baseline; ‡P < 0.05 versus rofecoxib 50 mg.

were analysed, as illustrated in Figure 3. It shows that the individual responses to lisinopril and rofecoxib were positively correlated \( R = 0.61 \) and \( R = 0.67 \), for 25 and 50 mg rofecoxib, respectively \( (P < 0.05) \). Thus, the patients with a favourable response to rofecoxib were also the ones in whom lisinopril was effective.

Side effects

Besides the effects on renal function, as described above, four patients reported adverse events. One diabetic and one non-diabetic patient complained of both dizziness and somnolence during indomethacin treatment. One diabetic and one non-diabetic patient newly developed peripheral pitting oedema during rofecoxib 50 mg treatment. No newly developed peripheral oedema was observed after the other treatment periods.

Discussion

This study demonstrates that, in patients with proteinuric renal disease from diabetic or non-diabetic origin, proteinuria was dose-dependently reduced by rofecoxib treatment.
This antiproteinuric effect was obtained without reduction of blood pressure. Treatment with the traditional NSAID indomethacin showed better antiproteinuric efficacy as compared to selective COX-2 inhibition with rofecoxib. Moreover, the ACE inhibitor lisinopril at maximal recommended dose was also more effective as compared to rofecoxib treatment. On the individual level, the antiproteinuric responses after rofecoxib and lisinopril treatment show a linear relation, indicating that patients with poor responsiveness to ACE inhibitor therapy seem not to benefit from the shift to selective COX-2 inhibition.

Proteinuria reduction is generally considered beneficial for renal outcome, and accordingly the antiproteinuric effect of rofecoxib can be interpreted as renoprotective. The evidence, however, for the renoprotective effects of proteinuria reduction is largely derived from studies on antihypertensive intervention in renal patients [1]. Those studies showed renoprotection by proteinuria reduction on top of the antihypertensive effects, in particular, by regimens based on RAAS blockade. Evidence for long-term renoprotection by specific proteinuria reduction without influencing blood pressure, however, is sparse. Before the era of RAAS blockade, two retrospective studies indicated an antiproteinuric effect of the traditional NSAID indomethacin associated with protection against long-term renal function loss [8,9]. No such data are available for rofecoxib or other selective COX-2 inhibitors. The evidence for protection against progressive renal damage by COX-2 inhibition so far is derived from studies in animal models for non-diabetic and diabetic nephropathy, showing that selective COX-2 inhibition reduces proteinuria as well as tubulo-interstitial and glomerular damage [14,20,21]. In order to confirm the renoprotective effect of COX-2 therefore, our current data on its antiproteinuric action would need long-term follow-up data.

Antihypertensive treatment is considered the cornerstone of renoprotective intervention. Yet, availability of tools for non-hypotensive proteinuria reduction may be useful. First, in some proteinuric patients, blood pressure is normal or low by nature [22]. Second, treatment strategies that lead to more complete blockade of the RAAS are associated with a high incidence of adverse events, such as hypotension (5). Third, a too low blood pressure may adversely affect renal outcome in the long term, as a recent meta-analysis showed a J-curved relation between systolic blood pressure and long-term renoprotection during ACE inhibition (6). Thus, aggressive blood pressure titration for proteinuria reduction apparently has its limits, indicating that non-hypotensive proteinuria reduction could be desirable under certain conditions.

We found a correlation between the individual responses to lisinopril and rofecoxib, indicating that good responding patients remain good responders after shifting to another class of antiproteinuric drug, whereas poor responders remain poor responders. This phenomenon has been observed previously and points towards the presence of therapy resistance in some individual proteinuric patients that seems to be determined by intrinsic patient factors [23]. Apparently, a therapy change into COX-2 inhibition is not a feasible strategy to overcome resistance to RAAS blockade-based therapy. It would be of interest to know whether the combination of COX-2 inhibition and lisinopril would be effective for this purpose, as the added antiproteinuric efficacy of the combination of traditional NSAID and ACE inhibition as well as limited data on the combination of selective COX-2 inhibition and ACE inhibition in membranous glomerulopathy suggests better antiproteinuric potential [24,25,26]. In contrast, in diabetic nephropathy, the addition of celecoxib to a maintenance regimen, consisting of quinapril or irbesartan and aspirin, did not alter proteinuria [27]. Due to preliminary withdrawal of rofecoxib from the market, we unfortunately could not address this issue.

Rofecoxib (at least at a dose of 50 mg) leads to a reversible rise in serum creatinine, similar to that after indomethacin. Older studies attributed (part of) the antiproteinuric effect of indomethacin to the decrease in GFR [7,12]. However, we found a reduction in fractional proteinuria, with both indomethacin and rofecoxib, indicating a specific antiproteinuric effect as well. A reversible decline in renal function at the onset of treatment has been assumed to indicate a drop in glomerular pressure that predicts a more favourable outcome in the long term [28], but it should be mentioned that the (non) selective interference in the prostaglandin system is associated with impairment of autoregulation of glomerular filtration that can facilitate acute renal failure under conditions of acute volume depletion. In addition, significant increases in serum potassium during rofecoxib treatment—be it within the normal range—were observed. The long-term renal consequences and safety of COX-2 inhibition obviously would need further study.

COX-2-derived prostaglandins (as PGE2) are important in modulating sodium excretion in the medulla [13,29]. As suggested by the increase in body weight, blockade of COX-2 seems to be associated with sodium and volume retention, leading also to increments of blood pressure and development of oedema—as experienced in two patients in our study after rofecoxib therapy [30,31]. Intriguingly, we found that these effects may be different between diabetic and non-diabetic patients. In particular, non-diabetic patients seem to be more vulnerable to increases in blood pressure due to sodium retention than diabetic patients. A possible explanation could be a different interaction between the prostaglandin pathway and the RAAS during COX-2 inhibition in hyperglycaemic patients. COX-2-derived PGE2 showed a decrease and renal haemodynamic function restored to normal after induction of normoglycaemia, indicating that the prostaglandin system may play a more prominent role in renal functional alteration during hyperglycaemia [32].

In non-renal patients having a history of colorectal adenoma, the APPROVe trial found a higher incidence of cardiovascular events in patients assigned to rofecoxib after chronic use exceeding 18 months, leading to premature closure of the trial and withdrawal of rofecoxib from the market [17]. Whether these observations are agent-specific effects or class-dependent effects, including selective COX-2 inhibitors as well as traditional NSAIDs, is currently subject to debate. One could argue that the cardiovascular risk is differently affected in the proteinuric patient, as rofecoxib and indomethacin have demonstrated to reduce proteinuria in our study. Proteinuria as such has been regarded as an
important cardiovascular risk factor [33–35], whereas proteinuria reduction is considered beneficial against progressive renal functional decline and subsequent cardiovascular risk. It should be noted that rofecoxib may raise blood pressure, influencing the cardiovascular risk it is associated with.

In the interpretation of our results, we acknowledge several limitations. First, this study was a proof-of-concept study in which only the short-term effects on proteinuria and renal function were studied. Second, since NSAID and ACE inhibitors have shown that a better antiproteinuric effect was established under conditions of correction of the volume excess, patients were instructed to adhere to a sodium restricted diet [7,10]. Most patients had, however, a higher salt intake than desirable that may have hampered the exploration of the antiproteinuric potential of rofecoxib, despite the standard background therapy consisting of hydrochlorothiazide in all patients. Third, due to preliminary withdrawal of rofecoxib, the pre-planned combination of RAAS blockade on top of rofecoxib on proteinuria could not have been studied. Thus, both efficacy and possible risks of combining the two strategies could not be established. Fourth, the patients studied in our study had a relatively preserved renal function and, consequently, an aggravate impact of rofecoxib on blood pressure, serum potassium and GFR in patients with worse renal function cannot be excluded.

We conclude that pharmacological intervention in the prostaglandin system by selective COX-2 inhibition is effective in non-hypotensive reduction of proteinuria. However, the translation to patient management is limited, as further exploration of rofecoxib is considered unethical based on the elevated cardiac risk in non-renal populations. Application of traditional NSAIDs for antiproteinuric treatment is limited due to high incidence of side effects and gastrointestinal complications. The study of other available selective COX-2 inhibitors, that share the profile of fewer side effects, may be helpful to expand the therapeutic arsenal for proteinuria reduction.

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References

Use of a first-line urine protein-to-creatinine ratio strip test on random urines to rule out proteinuria in patients with chronic kidney disease

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Abstract

Background. Urine protein strip tests are often used in the ward or clinic as first-line measures of proteinuria. The ability of a semi-quantitative meter-read strip test for the protein:creatinine ratio, Multistix® PRO® 10LS (Siemens Medical Solutions, Tarrytown, USA), was assessed as a first-line test to exclude significant proteinuria in the monitoring of patients with established chronic kidney disease. Methods. Eighty-six patients attending a hospital renal outpatient clinic collected three random urine samples during a 24-h period. Random urine protein:creatinine ratios measured by the strip test were compared to the laboratory estimation of 24-h protein excretion on that same day.

Results. At significant protein excretion of 0.3 g/24 h, the strips elicited negative predictive values in the range of 91.2–94.1% and negative likelihood ratios of 0.01–0.02, using all the random urines. Receiver–operator characteristic curve analysis also demonstrated good performance with all samples.

Conclusions. The strip test allows the physician to rule out significant proteinuria at the patient consultation on a random urine sample, obviating the need for specially collected samples, and with the added benefit of reducing the need for a lengthy and costly quantitative laboratory follow-up by ∼40–48%.

Keywords: chronic kidney disease; protein:creatinine ratio; proteinuria; urine strip tests

Introduction

Urine strip tests have been used for many years in the physician’s office and hospital clinic as first-line measures of the presence of proteinuria, in order to detect chronic kidney disease (CKD), while proteinuria is also an associated independent indicator of risk for cardiovascular disease. Thereafter, laboratory tests are generally performed to confirm and quantify the increased excretion of protein or albumin, in accordance with the recognized classification and guidelines for CKD [1–3], so that appropriate patient management can then be initiated.

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