The antiproteinuric effect of ace inhibition in renal disease

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CHAPTER 11

SUMMARY

THE ANTIPROTEINURIC EFFECT OF ACE INHIBITION IN RENAL DISEASE, THESIS.

Chapter 1

Chapter 1 is the introduction to this thesis. Proteinuria due to non-steroid-responsive renal disease may be harmful, firstly because it may cause a nephrotic syndrome, and secondly, since it is, like hypertension, associated with an increased risk of progressive renal damage and loss of renal function over years. Until recently, only non-steroidal anti-inflammatory drugs (NSAIDs) were available to reduce proteinuria in such patients. Due to their potential side effects, however, NSAIDs have never been widely used as antiproteinuric agents. In 1985 some studies were published showing that angiotensin converting enzyme (ACE) inhibition not only reduced the elevated blood pressure in animals with chronic renal failure (experimentally induced by renal ablation or by induced diabetic nephropathy), but also prevented the development of glomerular damage with proteinuria and loss of renal function. This beneficial effect of ACE inhibition was attributed to the prevention of glomerular hypertension. At the same time it was reported that ACE inhibition could reduce proteinuria in patients with advanced diabetic nephropathy. ACE inhibitors might thus be an attractive alternative for NSAIDs as antiproteinuric treatment, possibly being renoprotective and being generally well tolerated. The efficacy of the proteinuria lowering effect of ACE inhibition, and the mechanism of this effect, are studied in this thesis.

Chapter 2

In the first study of this thesis (chapter 2) the question is addressed whether ACE inhibition reduces proteinuria in 13 hypertensive patients with renal disease of various origin. Whereas conventional antihypertensive treatment (usually triple therapy) had, retrospectively, no significant effect on urinary protein excretion, ACE inhibition with lisinopril reduced proteinuria by approximately 60% after 12 weeks of treatment. This proteinuria lowering effect was not correlated with the fall in blood pressure nor with the approximately 20% reduction in GFR during lisinopril, whereas it did correlate with both the fall in renal vascular resistance and in filtration fraction, suggesting a postglomerular vasodilation with a fall in glomerular filtration pressure as a cause for the antiproteinuric effect of the ACE inhibitor.

Chapter 3

In chapter 3, the efficacy of the ACE inhibitor lisinopril in treating overt proteinuria is prospectively compared with that of the NSAID indomethacin in 12 patients with non-diabetic renal disease. Blood pressure lowering with α-methyldopa in the control periods had no effect on urinary protein excretion. During 10 week treatment periods, a lisinopril dose of (median) 5 mg per day, resulting in a blood pressure that was comparable to the value during α-methyldopa, reduced proteinuria by 27%, while a lisinopril dose of 10 mg per day reduced proteinuria by 50%. This anti-

proteinuric effect of lisinopril occurred irrespectively of initial proteinuria (ranging from 3.2 to 10.5 g/day), blood pressure (ranging from low-normal to elevated values), or renal function (with initial GFR ranging from 34 to 127 ml/min). In some patients it took several weeks before the proteinuria lowering effect of the ACE inhibitor reached a maximum and stabilized. The antiproteinuric effect of lisinopril was abolished when the sodium intake was increased from 50 to 200 mmol per day during lisinopril treatment, and proteinuria fell again when dietary sodium restriction was re-instituted. The antiproteinuric effect of the higher dose of lisinopril (median 10 mg per day) was comparable to the reduction in proteinuria during 150 mg per day of indomethacin. During indomethacin a reversible fall of 19% in GFR occurred, which was significantly more than the 7% decrease in GFR during lisinopril (see chapter 5), and the patients experienced more side effects during indomethacin than during lisinopril. Thus, the antiproteinuric effect of the ACE inhibitor lisinopril appears to be dose and time related, and is markedly dependent on dietary sodium restriction, whereas it does not depend on initial proteinuria, blood pressure, or renal function. The effect is comparable to that of indomethacin, while adverse effects are less.

Chapter 4

In chapter 4 the efficacy of the antiproteinuric effect of ACE inhibition in 10 diuretic treated patients with the nephrotic syndrome (mean proteinuria 10.5 g/day) is studied, as well as the effect of the combination of the NSAID indomethacin and the ACE inhibitor lisinopril. Both indomethacin and lisinopril monotherapy lowered proteinuria by more than 50% in 2-month study periods, while combination therapy further reduced proteinuria to less than 25% of the control values. Serum albumin rose during both monotherapies, without further increase on combination therapy. GFR showed a comparable reversible fall during indomethacin (of 15%) and lisinopril (of 12%) versus control. In parallel with the additive proteinuria lowering effect, combination therapy of indomethacin and lisinopril also additively lowered GFR (by 27%). Severe hyperkalemia (> 6.0 mmol/l) occurred in 3 patients during combination therapy. Thus, both indomethacin and lisinopril effectively reduce proteinuria in sodium depleted patients with the nephrotic syndrome. Moreover, combining these drugs results in an additive antiproteinuric effect, which may be useful in the symptomatic treatment of the nephrotic syndrome, but renal function and serum potassium should be monitored carefully.

Chapter 5

In chapter 5 the relevance is stressed, once more, of the changes in renal hemodynamics during ACE inhibition. Whereas, in general, no changes in serum creatinine are observed during treatment with an ACE inhibitor, we consistently detected a slight but significant decrease in GFR in our ACE inhibitor-treated patients with proteinuric renal disease. We showed that this effect of the ACE

inhibitor is influenced by the dose of the drug and by the sodium balance of the patients. The decrease in GFR during ACE inhibition reflects that GFR is dependent on adequate efferent glomerular vasoconstriction in sodium depleted patients with renal disease, like in patients with bilateral renal artery stenosis who also may show a fall in GFR during ACE inhibition, that can also be modulated by changing the dose of the ACE inhibitor or the sodium balance of the patients. In both groups of patients the fall in blood pressure cannot be compensated for as the renal autoregulation fails due the preferential postglomerular vasodilation during ACE inhibition, resulting in a fall in glomerular filtration pressure and in GFR. In parallel to the effects on GFR, the effect of ACE inhibition on proteinuria is also influenced by the dose of the drug and the sodium balance (see chapter 3). This favors the idea that the antiproteinuric effect of ACE inhibition is at least partially effected by a renal hemodynamic mechanism.

Chapter 6

The possible role of renal hemodynamic changes in the antiproteinuric effect of ACE inhibition is further elaborated in chapter 6, in which we show a positive correlation in different studies between the reduction in proteinuria and the fall in filtration fraction which probably reflects a fall in glomerular filtration pressure. Possible differences in response between diabetic and non-diabetic patients are discussed. In diabetics the blood pressure lowering as such contributes probably more to the antiproteinuric (and possibly renoprotective) effect of ACE inhibition than in patients with non-diabetic renal disease. In the latter blood pressure lowering as such is less effective and the characteristic renal hemodynamic effects of ACE inhibition are of relatively more importance.

Chapter 7

In chapter 7 the qualitative changes in proteinuria during ACE inhibition are studied, in addition to the quantitative changes as described in chapter 3. It appears that, like indomethacin, the ACE inhibitor lisinopril increases the selectivity of the residual proteinuria, since fractional clearances of proteins of greater molecular weight were more reduced during ACE inhibition than clearances of smaller proteins. This is interpreted as an increase in size permselectivity of the glomerular capillary barrier, due to the fall in intraglomerular filtration pressure or to inhibition of a direct effect of angiotensin II on the glomerular capillary filter. This increase in glomerular permselectivity may be part of the mechanism of the antiproteinuric effect of ACE inhibition.

Chapter 8

In chapter 8, the mechanism of the antiproteinuric effect of ACE inhibition is further studied by comparing the renal hemodynamic and antiproteinuric effects of indomethacin and lisinopril monotherapy and the combination of both drugs, in nine

patients with non-diabetic non-symptomatic proteinuric renal disease. The sequence of therapies is reversed in comparison to the study in chapter 4, which was performed in symptomatic diuretic treated nephrotic patients. Whereas both indomethacin and lisinopril lower urinary protein excretion, the hemodynamic profiles of these drugs are quite different: lisinopril lowers blood pressure and renal vascular resistance, inducing a fall in GFR while renal plasma flow is stable, which results in a fall in filtration fraction; indomethacin raises renal vascular resistance while GFR and renal plasma flow fall similarily, leaving the filtration fraction unchanged. Both hemodynamic profiles are compatible with a fall in intraglomerular capillary pressure: due to an afterload reduction during lisinopril by a preferentially postglomerular vasodilation, and due to a preload reduction during indomethacin by a preglomerular vasoconstriction. The antiproteinuric effect of both drugs can thus be attributed to a hemodynamic final common pathway, i.c. the decrease in glomerular filtration pressure. In accordance with this assumption, during combination therapy we observed (like in chapter 4) an additive decrease both in urinary protein excretion and in GFR, which were strongly correlated, presumably due to a simultaneous pre- and afterload reduction of the glomerular filtration pressure.

In accordance with the data in chapter 7, monotherapy with either lisinopril or indomethacin resulted in an increase in the selectivity of the residual proteinuria. However, no further improvement in selectivity occurred during combination therapy, whereas proteinuria fell by a further 58% after adding indomethacin to lisinopril. This observation raises doubt about the role of changes in glomerular permselectivity as cause of the antiproteinuric effect of these drugs.

Chapter 9

In chapter 9 the role of the hormone angiotensin II and the angiotensin II-mediated renal hemodynamic effects in the mechanism of the antiproteinuric effect of ACE inhibition is further investigated. The effects of different doses of exogenous angiotensin II (5%, 10% and 20% of the pressor dose) on renal hemodynamics and urinary protein excretion were studied in six non-diabetic normotensive patients with a mean proteinuria of 7.5 g/24 hr, both before and after three months treatment with the ACE inhibitor lisinopril. Lisinopril lowered proteinuria by more than 60% and induced a fall in blood pressure, renal vascular resistance and filtration fraction, whereas plasma angiotensin II levels and also angiotensin II pressor doses were unchanged compared to the pretreatment values. Angiotensin II infusion induced typical effects which appeared to be similar before and during lisinopril treatment: a dose-related fall in renal plasma flow and rise in systemic blood pressure, renal vascular resistance and filtration fraction, while the glomerular filtration rate remained relatively stable. However, neither before nor during lisinopril therapy did any changes in urinary protein loss occur during the infusions of angiotensin II, despite the fact that angiotensin II reversed the long-term systemic and renal hemodynamic effects of the ACE inhibitor. This observation argues against a direct

relation between the inhibition of angiotensin II synthesis and the resulting renal hemodynamic effects (with a fall in glomerular filtration pressure) on the one hand, and the reduction in proteinuria on the other during ACE inhibition. It is suggested that the long-term antiproteinuric effect of ACE inhibition may be the result of chronic hemodynamic effects causing structural changes that are not reversed by a short-term infusion of angiotensin II. Moreover, the inhibition of angiotensin II synthesis on the renal tissue level could play a role in the antiproteinuric effect of ACE inhibition, possibly through a non-hemodynamic mechanism of action.

Chapter 10

In chapter 10 a review is given of the data obtained from the studies described in the preceding chapters and from the literature, trying to answer the questions raised in the introduction of this thesis, regarding the efficacy and the mechanism of the antiproteinuric effect of ACE inhibition. New developments and future perspectives are indicated.

ANSWERS to the questions raised in the Introduction (Chapter 1, page 5).

SECTION I: Clinical efficacy:

1. ACE inhibition in general reduces proteinuria by 50%, which is comparable to the antiproteinuric effect of NSAID therapy.

2. a. The antiproteinuric effect occurs also in non-diabetic renal disease.
   b. The antiproteinuric effect is not influenced by pretreatment parameters such as initial blood pressure, renal function, and severity of proteinuria. Dietary sodium restriction, however, is necessary to optimize the proteinuria lowering effect of ACE inhibition.
   c. The effect of ACE inhibition on proteinuria is dose dependent. Moreover, the effect increases during the first weeks of treatment, in contrast to the immediate antiproteinuric effect of NSAID therapy.

3. Also in case of the nephrotic syndrome, ACE inhibition has been shown to reduce severe proteinuria in sodium depleted patients, resulting in an increase in serum proteins and in a clinical improvement.

4. Adding the ACE inhibitor lisinopril to the NSAID indomethacin (and vice versa) results in a further 50% reduction in proteinuria, to less than 25% of the pretreatment values. Renal function may, however, also additively decrease, and serum potassium may increase; both should therefore be monitored carefully!

SECTION II: Mechanism of action:

5. The antihypertensive effect may contribute to the antiproteinuric effect of ACE inhibition but cannot fully explain it, especially not in patients with non-diabetic renal disease, since blood pressure lowering with other antihypertensives did not lower protein excretion, and the effects on blood pressure can be dissociated from the effects on proteinuria during angiotensin II infusion.

6. The antiproteinuric effect of ACE inhibition is associated with, and may be caused by, the specific renal hemodynamic effects resulting in a fall in glomerular filtration pressure. However, since the long-term effects on proteinuria and on renal hemodynamics can be dissociated during short-term angiotensin II infusion, there is probably not a direct causal relation during prolonged treatment. The antiproteinuric effect of ACE inhibition may be the result of structural changes in the glomeruli, caused by a chronic reduction of glomerular capillary pressure or, alternatively, by non-hemodynamic effects.
   It is argued that the additive antiproteinuric effect of ACE inhibition and NSAID therapy is the result of a synchronous preload (by the NSAID) and afterload (by the ACE inhibitor) reduction of glomerular filtration pressure.

7. The antiproteinuric effect of ACE inhibition is probably associated with a functional improvement of the glomerular sieving properties (the size perm-selectivity), since the selectivity of the residual proteinuria increases during lisinopril treatment. This is, again, comparable to the effect of the NSAID indomethacin.

8. The long-term antiproteinuric effect of ACE inhibition does not directly result from the inhibition of angiotensin II formation, and appears to be independent of the plasma angiotensin II level.
   A role for angiotensin II in the antiproteinuric effect of ACE inhibition is, however, not excluded, since this effect may be caused by the (long-term) inhibition of renal tissue angiotensin II production, probably inducing both hemodynamic and non-hemodynamic (structural) changes in the glomeruli.