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Variability in therapeutic responses during interference in the renin-angiotensin system

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Summary

In order to slow the progressive decline in renal function often observed in patients with proteinuria, interference in the renin angiotensin system (RAS) has proven to be an effective mode of intervention. The renin angiotensin system can be affected on several levels of the cascade. The first step in activating the RAS is release of renin. Renin transforms angiotensinogen into angiotensin I. This step can be blocked by a renin-inhibitor. Angiotensin I is then converted into the active hormone angiotensin II by angiotensin-converting enzyme (ACE). The formation of angiotensin II can be blocked by an angiotensin converting enzyme inhibitor. Furthermore, interfering with the angiotensin receptor using an angiotensin II receptor antagonist can block the actions of angiotensin II. Angiotensin II is found as circulating hormone and is also formed in different organs such as the kidney. Angiotensin II is a potent vasoconstrictor both of the systemic and the renal vasculature. Formation of angiotensin II leads to an increase in systemic blood pressure and intraglomerular pressure. Furthermore, angiotensin II leads to an increase in tubular reabsorption of sodium. Angiotensin II is also a growth factor which promotes glomerular sclerosis and tubulointerstitial fibrosis. By interfering in the RAS blood pressure and urinary protein excretion are lowered. Furthermore, lowering the amount of urinary protein loss also results in an amelioration of the lipid profile, which is also thought to be unfavourable for the vasculature.

Over the last years a number of trials and meta-analyses showed the effectiveness of interference in the renin angiotensin system in lowering of proteinuria and preventing a rapid decline in renal function in both diabetic and non-diabetic renal disease. Unfortunately, in daily clinical practice we observed that the benefical responses on proteinuria and renal function could not be achieved in all patients. We questioned whether we could identify some of the mechanisms of such failure of therapy and how the efficacy of antiproteinuric therapy can be improved.

In chapter 1 we studied the effects on renal and systemic hemodynamics of an angiotensin-II receptor antagonist, candesartan cilexetil. Interference in the RAS sometimes results in a fall in glomerular filtration rate after onset of treatment. Although the initial fall in GFR is reversible, even after years of treatment, this has often been used as a reason not to start with an agent that interferes in the RAS system, especially in patients with a severely impaired renal function. In this study we compared the systemic and renal hemodynamic responses of candesartan cilexetil after onset of treatment and after 5 days treatment in patients with different degrees of renal function impairment. We found that most patients showed a favourable renal hemodynamic response, that is, an increase in effective renal plasma flow and a stable glomerular filtration rate resulting in

a decrease in filtration fraction. So, we concluded that the favourable short-term renal hemodynamic response of patients with severely impaired renal function implicates a beneficial response to treatment with an angiotensin-II receptor antagonist.

In chapter 2 we focus on the relationship between pharmacokinetics and pharmacodynamics of candesartan cilexetil in patients with different degrees of renal function impairments. We found that serum levels of the active metabolite candesartan were significantly higher in patients with impaired renal function compared to normal renal function. Furthermore, we found that candesartan cilexetil in the given doses resulted in a gradual decrease in blood pressure, which was significant in patients with severely to moderate renal function impairment. These results indicated that the pharmokinetic profile of candesartan cilexetil is affected by prevailing renal function. Candesartan cilexetil in a dose of 8 mg per day did not lead to symptomatic hypotension in patients with severe renal function impairment and seems a suitable dose for this group of patients. A higher dose of candesartan cilexetil is recommended for patients with a normal renal function.

The renin-angiotensin system exerts a circadian rhythm with maximal activity during daytime. We questioned whether interference in the RAS, given in the usual way, that is, once daily administration, will be equally effective in reducing blood pressure and urinary protein excretion both during the day and the night. In chapter 3 we showed that interference in the RAS with a renin inhibitor and with an ACE inhibitor resulted in a decrease in blood pressure and 24-hr protein excretion. The antihypertensive response during daytime was similar to the response during the night. The antiproteinuric efficacy was significantly better during daytime compared to nighttime. Earlier studies showed a dissociation between the diurnal rhythm of glomerular permeability characteristics and glomerular hemodynamics. So, an explanation for the differences found in hemodynamic and antiproteinuric responses may be that the mechanisms underlying nocturnal glomerular protein leakage are different from the mechanisms underlying daytime proteinuria. Another explanation could be that the pharmacokinetic or pharmacodynamic response of blood pressure is different from the response on proteinuria. To prevent renal function deterioration it is important to achieve a maximal antiproteinuric response all over the day. As nighttime proteinuria contributes to residual proteinuria, it is useful to find alternative therapeutic strategies to improve the lowering of proteinuria, such as alternative dosing schedules.

From studies performed in non-diabetic patients with proteinuria we know that there is a dissociation in time between hemodynamic and anti-proteinuric responses to interference in the RAS. The systemic and renal hemodynamic responses are fully present after start of therapy whereas the maximal anti-proteinuric response is seen after 4

weeks of treatment. This leads to the hypothesis that reduction of urinary protein excretion was not merely the result of changes in hemodynamics but the result of structural changes in the properties of the glomerula basement membrane. We questioned whether we would find the same phenomenon in patients with insulin-dependent diabetes mellitus and microalbuminuria treated with the angiotensin-I receptor antagonist losartan. We described in chapter 4 that losartan was effective in lowering urinary albumin excretion in patients with IDDM. The percentage reduction in albuminuria is comparable to treatment with an ACE-inhibitor. The antiproteinuric response was fully present within 7 days of treatment. Furthermore, the effects on renal hemodynamics and urinary albumin excretion showed a comparable pattern in time course. These results indicate that the lowering of urinary albumin excretion during interference in the RAS is closely related to the effects on renal hemodynamics rather than to structural, non-hemodynamic changes of the glomerular basement membrane in patients with insulin-dependent diabetes mellitus and microalbuminuria.

In chapter 5 we studied the efficacy of the antiproteinuric response of ACE-inhibition combined with a diuretic during a high sodium diet. Although the importance of sodium restriction in order to achieve a maximum antiproteinuric response is clear, it is very difficult for many patients to adhere to such a diet for a prolonged period of time. We showed that the adverse effects of a high sodium intake on antiproteinuric effect could be overcome by adding a diuretic to the medication. During fixed dose ACE inhibition, the amount of proteinuria during a low sodium diet was comparable to that during a high sodium diet combined with a diuretic. During ACE inhibition blood pressure increased after increasing the sodium intake and was lowered again after the diuretic was added. By depleting salt, either by sodium restriction of by a diuretic, the renin-angiotensin system is activated, which seems to be necessary to achieve a maximal response during interference of the renin angiotensin system. Furthermore, future clinical trials on the effects of interference in the RAAS should mention dietary sodium intake and the use of diuretics in order to make interpretation of the results valid and comparable.

As mentioned in the introduction, the dyslipidemia found in patients with proteinuria increases the risk of cardiovascular disease and, propably renal function decline. The amount of proteinuria is related to the degree of lipid derangement. In chapter 6 we reviewed clinical trials, originally performed to evaluate the effects of symptomatic antiproteinuric therapy, on the effect of antiproteinuric treatments on cholesterol levels. As the presence of hypercholesterolemia is a feature of the nephrotic syndrome, most studies mentioned total cholesterol levels in their results. We found that in all these trials the reduction in proteinuria was accompanied by a reduction in total serum cholesterol, with an estimation of 1 mmol/l serum total cholesterol lowering for every 4 gr/24hr urinary protein reduction. We found these responses during interference in the

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In chapter 7 we studied the effect on the plasma lipoprotein profile during treatment with an angiotensin-II recepor blocker in patients with insulin-dependent diabetes mellitus and microalbuminuria. Abnormalities in lipoprotein profile are often found in patients with IDDM with (incipient) nephropathy. These abnormalities in lipid composition become more evident once albuminuria develops. After 4 weeks treatment we found a significant decrease in total cholesterol, VLDL+LDL cholesterol and apo B levels, associated with a decrease in albuminuria. We found no changes in plasma cholestrol esterification and cholesteryl ester transfer and consequently no change in HDL-cholesterol. The amelioration of the lipoprotein profile may be beneficial in view of the increased cardiovascular risk and could contribute to renoprotection.

Future perspectives

Our goal is to optimize the symptomatic antiproteinuric treatment in order to lower urinary protein excretion as strict as possible. More effort should be made to reduce proteinuria in order to achieve a decline in the number of cardiovascular events and in the occurence of renal failure. In the present thesis a number of factors are identified to achieve this goal.

The presence of a severely impaired renal function is not a reason not to start with ACE-inhibition or angiotensin-II receptor antagonists. Our study showed that short-term treatment with an angiotensin II antagonist resulted in a favourable response of renal hemodynamics. A recent post-hoc analysis of the Ramipril Efficacy In Nephropathy (REIN) showed that interference in the RAAS slows glomerular filtration rate (GFR) decline over time and progression to end-stage renal disease in a safe way in patients with severely impaired renal function (GFR between 10 and 30 ml/min).

The importance of dietary measurements in the progression in renal function decline has been extensively studied for example in the Modification in Diet in Renal Disease study. Although the contribution of dietary measures is less outspoken when compared to the effects of interference in the renin-angiotensin system, the restriction in protein

intake can improve renal function outcome. Another important dietary measure is the restriction in sodium intake. In experimental renal injury, the kidney is more susceptible to injury during increased sodium intake. Furthermore, blood pressure, which is an important risk factor in the progression of renal function impairment, can be lowered by reducing the sodium intake both in participants with or without hypertension as shown in the DASH study (dietary approaches to stop hypertension). Especially during concomittant use of angiotensin-converting enzyme inhibition the importance of sodium restriction is eminent. We have shown that increasing the sodium intake can abolish the benefical effects of ACE-inhibition. Although it sounds oldfashioned, dietary advices and awareness of the importance of a balanced diet could very well contribute to better renal function outcome.

Over the last years a number of genetic polymorphisms of the renin-angiotensin-system are discovered. The most studied polymorphism is the angiotensin-converting enzyme insertion/deletion (I/D) polymorphism. These polymorphisms may be responsible for a different state of activity of the renin-angiotensin system. For example, higher levels of angiotensin-converting enzyme are found in patients with the ACE DD genotype polymorphism. This has led to the hypothesis that this genotype may be associated with a more rapid renal function decline. Until now several studies indeed have shown that the ACE DD genotype is associated with more rapid decline in renal function. This is not a consistent finding and confounding factors may be differences in race and environmental factors. Van der Kley showed that in proteinuric patients the interindividual variation in short-term response could not be explained by the ACE polymorphism. Interestingly, the relationship between responsiveness to ACE-inhibition and the ACE polymorphism was influenced by differences in prevailing sodium status. Furthermore, by changing the sodium intake the response to angiotensin I infusion can be modified in healthy volunteers with the DD genotype. Hopefully, further studies will give us more insight in the function and place of the different polymorphisms in either identifying the patients most at risk for development of renal failure or identifying the patients who will benefit most from our therapeutic strategies.

The pharmacological effects of drugs that interfere in the renin-angiotensin system are complex. An important reason for this complexity is the widespread presence of the angiotensin-converting enzyme and angiotensin-II receptors throughout the body. Angiotensin-II is a very potent vasoconstrictor and blockade of angiotensin-II results in a vasodilation of the systemic vasculature and within the glomerulus. Over the last years more functions of angiotensin-II have been discovered. Experimental studies have shown that angiotensin-II plays a role in the regulation of glomerular filtration rate, tubular transport and ultrafiltration. Furthermore, angiotensin-II is a renal growth factor and involved in collagen synthesis, modulation of nitric oxide release and immunomodulatory

functions. After start of interference in the renin-angiotensin system the hemodynamic responses are fully present after the first dose whereas the maximal antiproteinuric response is seen after several weeks of treatment. So, there is dissociation between the hemodynamic and non-hemodynamic structural responses. This could merely be a dissociation in time but this could also be the result of differences in pharmacokinetics between circulating and tissue located renin-angiotensin system.

Our group introduced the term 'titration for antiproteinuric effect'. The rationale for this approach is that the severity of proteinuria is associated with the rate of long-term renal function loss. In clinical practice, however, one generally evaluates the effect of interference in the renin angiotensin system on blood pressure rather than on proteinuria. By increasing the dose of the ACE-inhibitor or combining ACE-inhibitors with angiotensin-II receptor antagonists the antiproteinuric response can be optimized. Our group has found that this approach did not result in a further decrease in blood pressure and is a safe and practical approach to ensure maximal symptomatic antiproteinuric therapy in every individual patient. The effect on proteinuria of different timing of dosing over the day needs further study. So, more fundamental studies are needed to improve our understanding of the effects of angiotensin-II. These studies have to lead to clinical studies to improve the antiproteinuric response in patients with increased urinary protein excretion, both in non-diabetic and diabetic renal disease.