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Dual renin-angiotensin system blockade at optimal doses for proteinuria

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Background. The antiproteinuric effect of combining the angiotensin-converting enzyme (ACE) inhibitor lisinopril and the angiotensin II (Ang II) antagonist losartan was compared to that of the optimal antiproteinuric doses of monotherapy.

Methods. To this purpose, lisinopril and losartan were studied in 9 nondiabetic renal patients with median proteinuria 4.5 g/day (95% CI, 3.5, 6.4), creatinine clearance of 80 mL/min (95% CI, 66, 96), and mean arterial pressure (MAP) of 102 mm Hg (95% CI, 93, 112). First, in two protocols with six-week treatment periods per dose, the optimal antiproteinuric dose of each drug was established in each patient. Losartan and lisinopril were used in randomized order, each preceded by a baseline period without medication. The doses of losartan (mg/day) were 50, 100, 150, and again 50. The lisinopril doses were 10, 20, 40, and again 10. After the second protocol, patients were treated with a combination, using the optimal antiproteinuric doses established for the individual drugs.

Results. The antiproteinuric response by losartan was optimal at 100 mg (−46%; 95% CI, −60, −24%), being larger than at the 50 mg dose (−27%; 95% CI, −42, −4%, $P < 0.05$), but not different from the 150 mg dose (−46%; 95% CI, −58; −20%). Proteinuria decreased further at each up-titration step of lisinopril to −75% (95% CI, −85, −43%) at the 40 mg dose. Combination therapy reduced proteinuria more effectively (−85%; 95% CI, −96, −58) than monotherapy with losartan, and to a lesser extent than with lisinopril. Optimal blood pressure responses were obtained at similar doses.

Conclusions. Dose-titration with a renin-angiotensin system blocker, followed by add-on therapy is highly effective in order to reduce proteinuria. The safety of this regimen needs to be addressed in future studies.

Treatment with agents interfering in the renin-angiotensin system (RAS) retards the progressive course of chronic renal disease. The efficacy of angiotensin-converting enzyme inhibitors (ACEi) has been demonstrated both in diabetic [1] and non-diabetic renal disease [2]. The more recently introduced angiotensin II antagonists (Ang IIA) also are renoprotective, at least in type-2 diabetic nephropathy [3, 4].

Several lines of evidence indicate that the renoprotective efficacy of RAS-blocking agents is related to their antiproteinuric properties. The antiproteinuric response to intervention is the strongest predictor of long-term renoprotective efficacy [5–7]. Evidence from large clinical trials is now available showing that residual proteinuria during treatment is an independent risk factor for progression of renal disease. Thus, reduction of proteinuria should be an independent therapeutic target [8]. Consequently, the focus of renoprotective intervention has shifted toward optimal reduction of proteinuria, in addition to control of blood pressure [9, 10].

Treatment schedules should be developed that afford optimal reduction of proteinuria in addition to blood pressure control. Considering the consistent antiproteinuric effects of RAS-blocking agents, the first step should be to establish the optimal treatment schedule for reduction of proteinuria using these drugs.

First, dosing is important. The recommended doses of ACEi and Ang IIA are derived from hypertension trials, but the dose-response for the antiproteinuric effect may not be similar to the dose-response for blood pressure. For example, animal experiments showed that doses of ACEi and Ang IIA higher than needed for optimal blood pressure control, provided additional renoprotection [11]. Unfortunately, dose-finding studies for proteinuria in humans are scarce [12, 13]. Moreover, it is well recognized that the dose needed to reach a blood pressure target can be different between patients, and it would be relevant to see whether this also applies to reduction of proteinuria.

Second, simultaneous blockade of the RAS at different levels may result in improved efficacy compared to monotherapy. Because of generation of angiotensin II

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via non-ACE pathways [14], monotherapy with an ACEi could result in suboptimal blockade of the RAS, even at the maximally effective dose. On the other hand, blocking the angiotensin II type 1 (AT1) receptor by monotherapy with an Ang IIA results in a compensatory rise in renin, and consequently Ang II, with so far unknown consequences.

Thus, in order to improve antiproteinuric therapy both optimization of the dose and dual blockade of the RAS may be fruitful. Several studies have investigated dual RAS blockade in nondiabetic [15, 16], diabetic [17] or mixed renal patients [18], with promising, but not uniform results.

None of these studies tested whether the applied doses of both drugs were on the top of the dose-response for proteinuria. Consequently, an observed added effect of the combination also might have been obtained by monotherapy at a higher dose. Therefore, in the present study, we first aimed to establish the optimal antiproteinuric dose for monotherapy with the ACEi lisinopril and the Ang IIA losartan for individual renal patients with nondiabetic proteinuria. Subsequently, patients were treated with a combination of the optimal dose of both drugs to test whether this results in a stronger reduction of proteinuria than either drug alone.

METHODS

Patients and protocol

Patients were selected from our renal outpatient department. All patients gave informed consent and, after at least six weeks without antihypertensive medication, fulfilled the following inclusion criteria: stable proteinuria $\geq$2 g/day and diastolic blood pressure between 80 and 110 mm Hg, a creatinine clearance $\geq$30 mL/min/1.73 m^2 and age between 18 and 70 years. Patients with cardiovascular disorders or diabetes mellitus were excluded, as well as frequent users of non-steroidal anti-inflammatory drugs (NSAIDs; >2 doses/week).

This outpatient study was performed open-label and the patients were instructed to take the study medication once daily, in the morning, except on the study days: on those days the study drug was taken after the hospital visit, so blood pressure was measured at trough. During the period of combined treatment, lisinopril was taken in the evening and losartan was taken in the morning. Patients were instructed to adhere to a dietary sodium-restriction of 5 to 7 g/day.

The study consisted of two titration protocols with the respective monotherapies in randomized order. Before both titration schedules, there was a baseline period without medication. All treatment periods, including the two baseline periods, lasted six weeks. The consecutive daily doses in the losartan protocol were 50 mg, 100 mg, 150 mg and 50 mg. In the lisinopril protocol, the daily doses were 10 mg, 20 mg, 40 mg and 10 mg. Immediately after completing the second protocol, patients were treated for six weeks with the combination of both drugs. To that purpose, each drug was administered at the dose that had rendered optimal antiproteinuric efficacy in that individual patient.

Clinical and laboratory procedures

Blood pressure was measured at every visit under similar conditions, at trough at one minute intervals by a Dinamap®, with the patient in supine position. After fifteen minutes of measurements, the mean of the last four readings was used for further analysis. Mean arterial pressure (MAP) was calculated as the sum of one-third systolic and two-thirds of the diastolic blood pressure. Urinary protein was determined using the pyrogallol red-molybdate method. At the end of each period, patients collected urine for two consecutive days. Daytime and nighttime samples were collected separately by the patients. The general results on proteinuria were obtained from the 24 hour amounts. In addition, the relative day- and nighttime efficacy of proteinuria reduction was compared between both drugs. To this end, day/night ratios (in duplicate, corrected for creatinine) were calculated at baseline and at each dose of both drugs. Serum and urinary electrolytes, uric acid and creatinine were determined using an automated multi-analyzer (SMA-C®; Technicon, Tarrytown, NY, USA).

Data analysis

Results are expressed as median and 95% confidence intervals (95% CI). Blood pressure is expressed as mean arterial pressure. Proteinuria at the end of each period is represented as residual proteinuria and as percentage change from baseline (mean of two baseline values). For each patient, the lowest level of proteinuria, obtained during monotherapy with losartan and lisinopril was established. Then, the Wilcoxon Signed Ranks Test was used to test whether these values differed from combined therapy. Differences were considered significant if the P value was <0.05. Previously, we calculated that a sample size of $N = 10$ is needed to detect changes in proteinuria of 0.5 g/day with expected standard deviation of 0.5 g/day with a desired power of 0.8 and alpha 0.05 [13].

RESULTS

Patient characteristics

Ten consecutive patients were included, all of whom were middle-aged Caucasians. One patient was not able to maintain scheduled visits and was excluded. The nine patients who completed the entire protocol had mildly

Table 1. Patient characteristics (without medication, median and 95% CI or number)

Male/female	6/3
Age *years*	51 (44; 55)
Creatinine clearance *mL/min*	80 (66; 96)
Supine blood pressure *mm Hg*	
Systolic	137 (130; 152)
Diastolic	80 (73; 89)
Diagnosis	FSGS (4), MGP (3), IgA (1), NCBx (1)
Previous medication	ena (6), ena/hct (1), lis/hct (1), los (1)

Abbreviations are: FSGS, focal and segmental glomerulosclerosis; MGP, membranous glomerulopathy; IgA, IgA nephropathy; NCBx, non-conclusive biopsy; ena, enalapril; hct, hydrochlorothiazide; lis, lisinopril; los, losartan.

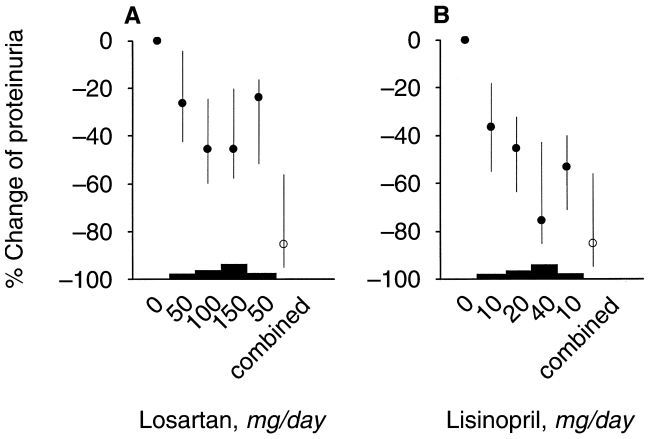

Fig. 1. Response of proteinuria according to the dose of losartan (*A*) or lisinopril (*B*) in nine non-diabetic renal patients. Data are median, 95% CI. Note that the response to combined therapy (○) is the same value in both panels. Responses are expressed as % change from baseline. The baseline value was calculated as the mean of two six-week periods without medication. All doses resulted in a significant change from baseline.

to moderately impaired renal function and were normotensive without medication (Table 1).

Proteinuria during treatment with losartan, lisinopril and the combination

Baseline proteinuria was 4.5 g/day (95% CI, 3.5, 6.4). In the losartan protocol, maximal antiproteinuric efficacy was obtained with the 100 mg dose (Fig. 1A), corresponding to a residual proteinuria of 2.8 g/day (95% CI, 1.5, 4.6). Increasing the dose to 150 mg/d did not further reduce proteinuria (2.6 g/day; 95% CI, 1.5, 4.9). After down-titration of losartan from 150 to 50 mg/day, proteinuria increased to 3.3 g/day (95% CI, 1.9, 4.8), which was not different from the first 50 mg dose period (3.3 g/day; 95% CI, 2.1, 5.8), demonstrating stability of the proteinuric condition during the time course of the protocol.

Dose-titration with lisinopril revealed a different pattern (Fig. 1B), as each up-titration step resulted in a further reduction of proteinuria. Residual proteinuria after lisinopril 40 mg/day was 1.4 g/day (95% CI, 0.5, 3.2), which was significantly lower, not only than residual proteinuria after lisinopril 20 mg/day (2.2 g/day; 95% CI, 1.5, 3.6) and lisinopril 10 mg/day (3.3 g/day; 95% CI, 1.7, 4.8), but also than losartan 150 mg/day. After down-titration of lisinopril from 40 to 10 mg/day, proteinuria remained significantly lower (2.0 g/day; 95% CI, 1.1, 3.5) than after the first treatment period with lisinopril 10 mg/day.

After completing the second titration protocol, patients were simultaneously treated with both drugs at their individual optimal antiproteinuric dose. Combined therapy consisted of losartan 150 mg and lisinopril 40 mg in three cases, losartan 100 mg and lisinopril 40 mg in two cases, losartan 100 mg and lisinopril 20 mg in two cases, and losartan 50 mg and lisinopril 40 mg in two cases. Combined treatment with lisinopril and losartan resulted in an antiproteinuric response that was significantly stronger than monotherapy with losartan or lisinopril (Fig. 1 and Table 2).

The day/night ratio of proteinuria at baseline was 1.5 (1.1; 1.6). This ratio did not change during therapy. The ratios obtained with losartan were 1.4 (1.2; 2.0), 1.3 (1.0; 2.0), 1.6 (1.3; 2.1) and 1.5 (1.3; 2.2) for the consecutive treatment periods, respectively. The day/night ratios with lisinopril were similar, 1.4 (1.1; 2.1), 1.4 (1.0; 2.5), 1.5 (0.8; 2.2) and 1.4 (0.9; 2.2). After combined treatment, the ratio was 1.5 (1.1; 2.3). Thus, the relative antiproteinuric efficacy during day and night was similar for both drugs individually and for the combination.

Blood pressure during treatment with losartan, lisinopril and combination therapy

Baseline mean arterial blood pressure was 102 mm Hg (95% CI, 93, 112). Blood pressure was lowered by all doses of losartan and lisinopril (Fig. 2). The differences in MAP after losartan 50 mg/day (92 mm Hg, 95% CI, 89, 96), losartan 100 mg/day (87 mm Hg, 95% CI, 83, 95) and losartan 150 mg/day (89 mm Hg, 95% CI, 79, 97) were not statistically different. During dose-titration with lisinopril, the lowest MAP was achieved with the 40 mg dose (77 mm Hg; 95% CI, 74, 92). This was significantly lower than MAP after lisinopril 10 mg/day (90 mm Hg, 95% CI, 81, 96), but non-significantly different from lisinopril 20 mg/day (82 mm Hg, 95% CI, 80, 94). Combination therapy lowered MAP to a level lower than the optimal dose of losartan, but not different from the optimal dose of lisinopril (Table 2).

Adverse events

None of the patients dropped out of the study because of adverse drug effects. Nevertheless there were a few cases of dizziness and hyperkalemia (Table 2).

DISCUSSION

The present study first showed that agents interfering in the RAS cause a dose-dependent decrease of protein-

Table 2. Median (95% CI) of parameters at baseline, after the optimal dose of monotherapy (losartan, lisinopril) and after combination therapy

	Baseline[a]	Losartan	Lisinopril	Lis + Los
U_{prot} *g/day*	4.5 (3.5; 6.4)	2.2 (1.2; 4.8)[b]	1.4 (0.5; 2.9)[bc]	1.0 (0.0; 2.6)[bcd]
MAP *mm Hg*	102 (93; 112)	88 (81; 98)[b]	77 (74; 90)[bc]	77 (73; 85)[bc]
C_{Cr} *mL/min*	80 (66; 96)	73 (59; 89)	72 (52; 92)	66 (51; 80)[b]
BW *kg*	76 (69; 85)	78 (70; 87)	74 (70; 84)	75 (70; 84)
U_{Na} *mmol/day*	121 (75; 182)	113 (75; 143)	109 (72; 139)	101 (69; 138)
S_{UA} *mmol/L*	0.43 (0.39; 0.47)	0.43 (0.40; 0.46)	0.49 (0.44; 0.53)	0.46 (0.41; 0.51)
S_{chol} *mmol/L*	6.0 (5.5; 6.6)	6.0 (5.0; 7.0)	5.8 (5.3; 6.3)	5.5 (5.1; 5.9)
S_K >5.5 *N*	0	1	2	2
Dizziness *N*	0	1	1	2

Abbreviations are: U_{prot}, proteinuria; MAP, mean arterial pressure; C_{Cr}, creatinine clearance; BW, body weight; U_{Na}, urinary sodium excretion, S_{UA}, serum uric acid, S_{chol}, serum cholesterol, S_K, serum potassium.

[a] Mean of two baseline periods

[b] $P < 0.05$ vs. baseline

[c] $P < 0.05$ vs. optimal dose of losartan

[d] $P < 0.05$ vs. optimal dose of lisinopril

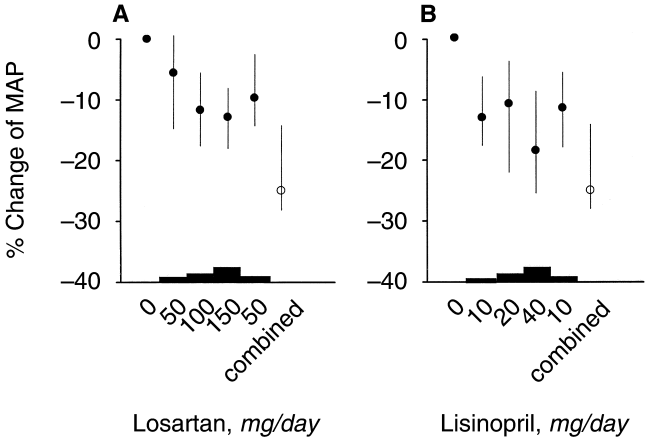

Fig. 2. Response of mean arterial pressure (MAP) to the dose of losartan (*A*) or lisinopril (*B*) in nine non-diabetic renal patients. Data are median, 95% CI. Note that the response to combined therapy (○) is the same value in both panels. Responses are expressed as % change from baseline. Baseline value was calculated as the mean of two six-week periods without medication.

uria. Second, the combination of the ACEi lisinopril and the Ang IIA losartan at their maximally effective dose caused an additional reduction in proteinuria and blood pressure. To our knowledge, this is the first study showing an added effect of dual RAS blockade taking into account the dose-response of the respective monotherapies.

Our study was designed to establish the optimal strategy for reduction of proteinuria with RAS blockers. To that purpose, we first investigated the effect of increasing the dose of the ACEi lisinopril and the Ang IIA losartan. Importantly, the optimal antiproteinuric dose differed per individual, implicating that the responsiveness to antiproteinuric intervention displays interindividual differences. The importance of individual factors in drug response is increasingly recognized [19, 20]. Several factors could be involved in the differences. For instance, it could be speculated that the pharmacokinetics of a certain drug are different because of patient factors such as the genetic background (for example, polymorphisms of RAS components) or type and severity of the renal disease. However, because of its small size, the present study is not well suited to analyze determinants of the response variability.

Increasing the dose of lisinopril resulted in a progressive decline of proteinuria at each up-titration step, suggesting that 40 mg/day was not on the top of the dose-response. Dosing beyond 40 mg/day may even be more effective than the obtained 75% reduction. However, the blood pressure levels obtained were already very low and the tolerability of higher doses is a concern, especially in normotensive patients. The maximum antiproteinuric response to losartan, which was already obtained at the 100 mg dose, was less effective than to lisinopril. Findings for blood pressure were similar. Since this study was not designed to compare both drugs, additional studies are necessary to put this finding into the proper perspective. For a complete titration schedule, for instance, a 200 mg dose of losartan should have been used, that is, doubling of the dose at each up-titration step analog to the lisinopril schedule. However, unfortunately no toxicity data on high doses of losartan were available to justify such a study design.

At the group level, lisinopril lowered both proteinuria and blood pressure somewhat more effectively than losartan. This was not the result of a difference in duration of action, given our results on day- and nighttime proteinuria. It may be that the differences in antiproteinuric efficacy are due to different blood pressure control. However, no clear-cut correlation between both parameters was found, which is consistent with the literature that RAS blocking agents have antiproteinuric effects independent of the blood pressure response [21–23]. To date the mechanism of the antiproteinuric action is incompletely understood. Whereas a lower systemic blood pressure contributes to the reduction in proteinuria, blood

pressure and proteinuria also could be independent reflections of the therapeutic efficacy of lisinopril.

This study tested the combined effects of an ACEi and an Ang IIA, taking into consideration the optimal antiproteinuric dose of the single agents. The combination had a considerably stronger antiproteinuric and antihypertensive effect than monotherapy losartan. In comparison to the highest tested dose of the ACEi, the combination also provided an antiproteinuric response that was somewhat stronger. However, we cannot exclude the possibility that increasing the dose of lisinopril would have rendered a similar result, and it cannot be established from our data whether addition of Ang IIA to ACEi dosed at its maximally effective dose would have resulted in an added effect. We recently found that addition of Ang IIA to ACEi at the well-established top of its dose-response failed to enhance the therapy-response in experimental nephrosis [24].

Importantly, the doses were increased in six-week treatment periods without washout periods between the treatment periods. It has been demonstrated previously that the antiproteinuric response stabilizes after approximately four weeks [25]. This protocol was deliberately chosen because, rather than testing the effect of a dose per se, the approach of up-titration itself is important to obtain the optimal reduction of proteinuria. Thus, although less relevant for clinical practice, the possibility of carry-over should be considered. In case of losartan, carry-over effects seem absent, as blood pressure and proteinuria levels in the first dosing period were similar to those measured after down-titration during the last period. With lisinopril, blood pressure completely recovered during the down-titration period, whereas recovery of proteinuria amounted to about two-thirds. However, a carry-over effect with lisinopril is unlikely to confound the results on proteinuria during combined treatment. Although the down-titration period did not result in a complete recovery of proteinuria to baseline values during the study period, levels dropped to those observed at 20 mg lisinopril. As all patients received at least 20 mg lisinopril during the combination treatment period, the influence of suboptimal recovery of proteinuria seems limited.

No other renoprotective or antihypertensive drugs were used. It is well established that the antiproteinuric and antihypertensive effect of both ACEi and Ang IIA is improved with concomitant diuretic treatment of sodium restriction [26, 27]. It would therefore be worthwhile to test whether further optimization of the antiproteinuric response could be obtained by combining a dual RAS blockade with a diuretic and/or more rigid sodium restriction.

Although the importance of titration according to the antiproteinuric response has been recognized [9, 10], dose-response studies with ACE inhibitors or Ang II antagonists are scarce. To our knowledge, only one study in patients with IgA nephropathy reported on the antiproteinuric effect of increasing doses of lisinopril [12]. Proteinuria progressively decreased from 1.8 g/day to 0.6 g/day with increasing the lisinopril dose up to 20 mg/day. Although proteinuria did not fully recover between the treatment periods, the antiproteinuric response to lisinopril seemed dose-dependent in the lower dosing-range. Our current study shows that further increasing the dose of lisinopril to 40 mg/day results in a considerable additional reduction. With respect to Ang IIA, two reports indicated that the optimal dose of losartan is 100 mg/day in both diabetic (abstract; Andersen et al, *J Am Soc Nephrol* 11:112A, 2000) and non-diabetic renal patients [13]. On the other hand, the use of supramaximal doses of the Ang IIA candesartan appeared promising in another study [28]. Thus, the dosing-issue, especially with respect to potential differences between Ang II antagonists, needs to be further elucidated in future research.

Increasing the dose of the individual drugs prior to the combination treatment effectively improved the antiproteinuric response. Some other studies have applied a dual RAS blockade from a somewhat different perspective. For example, in patients with IgA nephropathy, there was additional antiproteinuric effect of adding losartan to a deliberately chosen sub-hypotensive dose of an ACEi [15], and the combination of relatively low doses of losartan and enalapril were more effective than a somewhat higher dose of either monotherapy [16]. This is important, since combining low doses may have the benefit of fewer side effects. A well-designed study in primarily African American diabetic patients found no additional antiproteinuric effect by adding losartan 50 mg to lisinopril 40 mg [18]. These were therapy-resistant patients with uncontrolled blood pressure despite the use of several antihypertensive drugs, suggesting that differences between the studied populations exist, such as less efficacy of the RAS blockade in African Americans [29], which could be important determinants of the therapeutic response. Finally, whether an additional reduction of proteinuria is found in add-on schemes also could be determined by the order of application of the drugs, as was indicated by our own findings.

None of our patients dropped out of the study because of side effects. Nevertheless, the small size of the present study does not allow conclusions on safety and/or tolerability. The risk for hypotension or hyperkalemia during combined ACEi and Ang IIA at high doses especially needs to be evaluated.

In summary, RAS blockers have a dose-response for proteinuria and the combination of the ACEi lisinopril and the Ang IIA losartan was clearly more effective in reducing proteinuria than the maximally effective dose of losartan. Dual blockade was also somewhat more effective than lisinopril, but further studies should be conducted to establish whether an additional reduction of

proteinuria could safely be obtained by supramaximal doses of lisinopril. In conclusion, dose-titration with a RAS blocker followed by add-on therapy is a highly effective approach to reduce proteinuria. The safety of combined therapy at high doses needs to be addressed in future studies.

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