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Combination is better than monotherapy with ACE inhibitor or angiotensin receptor antagonist at recommended doses

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Abstract

Objective

The combination of an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin II (Ang II) receptor antagonist (ARB) could provide a higher degree of blockade of the renin-angiotensin system (RAS) than either agent alone. The primary aim of this study was to look at the effect of three therapeutic regimens (titrated ACE inhibitor (ACE-I) versus titrated ARB versus the combination of an ACE-I and an ARB) on the attainment of adequate blood pressure (BP) control and antiproteinuric effect. Both ACE-I and ARB were titrated as monotherapy up to the maximal recommended dose.

Methods

A pilot randomised, parallel group open-label study was conducted in 36 patients with primary renal disease, proteinuria above 1.5 g/day and BP >140/90 mmHg while on therapy with an ACE-I. Patients were randomly assigned to (1) benazepril, n=12; (2) valsartan, n=12; or (3) benazepril plus valsartan, n=12. Other antihypertensive therapies could also be added to attain goal BP (<140/90 mmHg). The primary endpoint was the change in proteinuria during six months of follow-up.

Results

In the presence of similar BP decreases and stable creatinine clearance values, mean proteinuria decreases were 0.5 ± 1.7 , 1.2 ± 2.0 and 2.5 ± 1.8 g/day in groups 1, 2 and 3, respectively. When compared with baseline values, only the fall induced by the combination of ARB and ACE-I attained statistical significance ($p < 0.05$).

Conclusion

The antiproteinuric capacity of monotherapy at recommended doses with either an ACE-I or an ARB is lower than that obtained with the combination of the two drugs.

Introduction

The administration of angiotensin-converting enzyme (ACE) inhibitors has proven to be effective in reducing proteinuria in diabetic^{1,2} and non-diabetic^{3,4} nephropathies, and in slowing the rate of progression of chronic renal failure.^{5,7} ACE is a pluripotent enzyme that catalyses the conversion of angiotensin I into angiotensin II (Ang II), while

impeding degradation of bradykinin and other vasoactive peptides.⁸ ACE-I do not interfere with the production of Ang II by non-ACE-dependent pathways^{9,10} and an escape of Ang II from the effects of ACE inhibition has been described during chronic therapy.^{11,12}

Most of the known physiological and pharmacological actions of Ang II are mediated by the AT₁-receptor subtype, including its cardiovascular, central nervous system, and renal actions.¹³ Angiotensin receptor blockers (ARBs) impede Ang II from coupling to the AT₁-receptor and so the effects of Ang II on cardiovascular and renal systems do not take place. Thus, ARBs differ from ACE-I, since they compete with the effector hormone of the RAS for the Ang II receptor, without increasing bradykinin.¹⁴ Initial studies performed in human¹⁵⁻¹⁸ demonstrated a capacity of ARBs to reduce microalbuminuria-proteinuria, which was apparently similar to that of ACE-I during short-term therapy. Recently, ARBs have been shown to protect renal function in Type 2 diabetes mellitus.¹⁹⁻²¹

Recent evidence shows that the combination of an ACE-I and an ARB is safe in terms of renal function and for the development of hyperkalaemia²² and that it could improve blood pressure (BP) control²³⁻²⁶ and reduce proteinuria.^{27,28} However, the possibility that up-titration, probably over the usual higher recommended dose, of any of the two monotherapies is as effective remains to be analysed.

The primary aim of the study was to investigate in daily clinical practice the effects of monotherapy with an ACE-I or an ARB up-titrated to the maximal recommended doses by the Physicians Desk Reference, and to compare it with that of the combination of the two drugs on proteinuria during a follow-up of six months.

Methods

Study population

Thirty-six patients were randomised, 26 male (72%), mean age 49 ± 15 years, diagnosed as having primary renal disease and presenting BP >140/90 mmHg and proteinuria >1.5 g/day while on therapy with an ACE-I alone or in combination with other antihypertensive drugs for at least three months, and creatinine clearance values >30 ml/minute.

Table 1 Demographic baseline data, showing no differences between groups

| | Benazepril (n=12) | Valsartan (n=12) | Combination (n=12) |
|----------------------------------|----------------------|---------------------|-----------------------|
| Age (years) | 49.8±16.5 | 49.7±12.4 | 47.9±15.2 |
| Sex (M/F) | 8/4 | 8/4 | 10/2 |
| Weight (kgs) | 75.7±7.8 | 82.8±17.4 | 78.3±15.8 |
| Height (cms) | 166±9 | 166±8 | 170±9 |
| SBP (mmHg) | 154±16 | 152±21 | 149±15 |
| DBP (mmHg) | 94±10 | 89±10 | 87±10 |
| Heart rate (bpm) | 86±8 | 82±6 | 82±6 |
| Creatinine clearance (ml/minute) | 72±25 | 74±23 | 68±29 |
| Proteinuria (g/24-hour) | 3.8±2.4 | 4.6±3.4 | 4.1±2.4 |

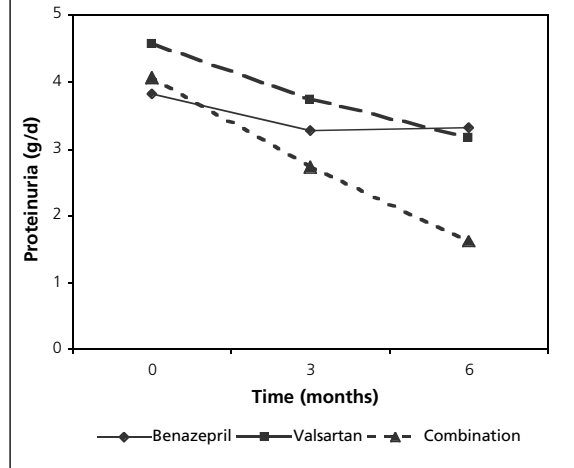
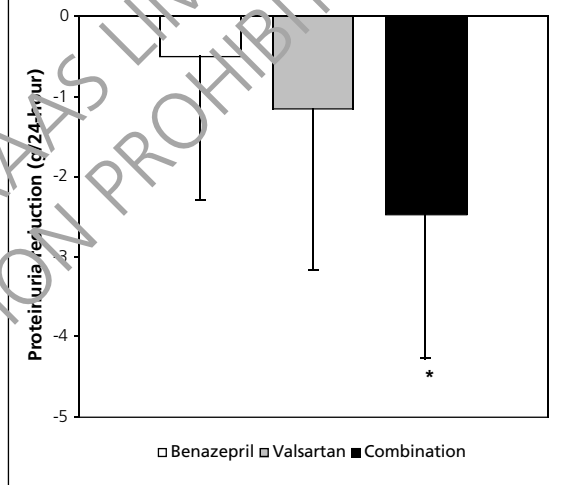
SBP = systolic blood pressure; DBP = diastolic blood pressure; bpm = beats per minute

Study design

We used a prospective, randomised, and open design. After discontinuation of ACE-I therapy, we randomly assigned patients to any of the three therapeutical arms: Group 1; benazepril, Group 2; valsartan, and Group 3; benazepril plus valsartan. Group 1 received benazepril, 10–20 mg daily, according to renal function (patients with creatinine clearance below 50 ml/minute received 10 mg daily, and those with higher values received 20 mg daily). Group 2 received valsartan, 80 mg, titrated two weeks later to 160 mg daily. Group 3 received benazepril, 10–20 mg daily according to renal function, during the first four weeks and valsartan, 80 mg daily, was then added and, if needed, titrated to 160 mg daily four weeks later. Titration up to the maximal recommended doses was forced and other non ACE-I, non-ARB antihypertensive therapies (loop diuretics, β -blockers, doxazosin) could be added thereafter if needed to lower BP to values below 140/90 mmHg. At the first and follow-up visits, systolic and diastolic BP was measured three times after five minutes of rest, with a mercury sphygmomanometer, and blood and 24-hour urine samples were collected to measure creatinine clearance, serum potassium, proteinuria and natriuresis. The local Ethics Committee approved this study protocol and all patients gave their informed written consent to participate.

Statistical analysis

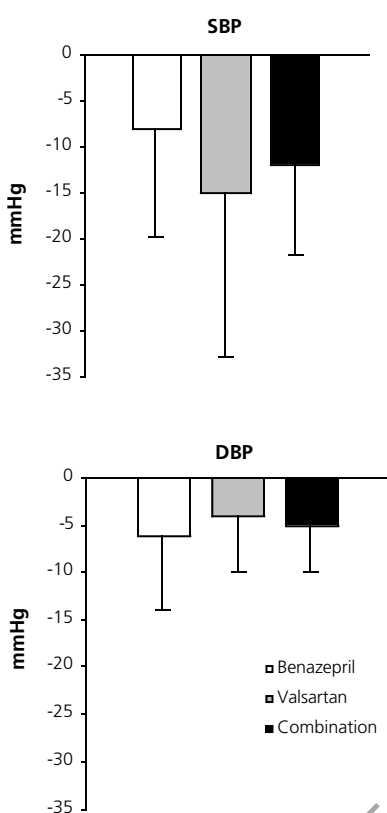
T-test and χ^2 -test were used to compare quantitative and qualitative variables, respectively. Changes in continuous variables from baseline values, by treatment group, were analysed by Anova, adjusted for the baseline value. Data are expressed as mean±standard deviation. After six months of treatment, protein excretion and BP reduction were calculated as the difference between final and baseline values for each patient.

Figure 1 Evolution of proteinuria during follow-up**Figure 2** Reduction of proteinuria after treatment. Data are expressed as mean reduction±standard deviation. * p<0.05 compared with benazepril group

Results

Table 1 shows the demographic baseline data, showing no differences between groups. Baseline protein excretion values were 3.82±2.4 g/24-hour in group 1, 4.56±3.4 g/24-hour in group 2, and 4.01±2.4 g/24-hour in group 3 (p NS). These values were 3.28±2.3, 3.74±2.5 and 2.74±2.3 g/24-hour at month three, and 3.32±2.3, 3.16±2.9 and 1.61±1.7 g/24-hour after six months, respectively (Figure 1). Mean protein excretion decreases were 0.5±1.7, 1.2±2.0 and 2.5±1.8 g/24-hour in groups 1, 2 and 3, respectively (p<0.05 between group 1 and 3) (Figure 2). A significant fall in BP was attained in the three groups after six months of therapy: mean systolic BP decrease was 8±10 mmHg in group 1, 15±18 in group 2, and 12±11 mmHg in group 3; mean diastolic BP decrease was 6±5, 4±6 and 5±8 mmHg, respectively. The BP reduction was similar for the three groups, except that systolic BP was significantly lower in group 2 when compared with group 1 at three and six months (Figure 3). The percentages of patients

Figure 3 Reduction of systolic blood pressure (SBP) and diastolic blood pressure (DBP) after six months of treatment. Data are expressed as mean reduction \pm standard deviation



with adequate BP control were similar between the three groups during the follow-up (Table 2). Table 3 shows the evolution of natriuresis, serum potassium and creatinine clearance, that did not change during the follow-up period.

Discussion

Strict BP control, together with as large as possible diminution of proteinuria, are the main tools to stop or to slow the velocity of decline in renal function in renal diseases presenting with high BP and proteinuria.²⁹ The present study has tried to reflect what could have been done in daily clinical practice when patients already treated with an ACE-I, alone or in combination, present with inadequate control of BP and proteinuria. The first possibility is to titrate to maximum doses the ACE-I, adding other therapies to control BP. Secondly, it is possible to switch therapy to an ARB and to titrate the dose to the maximal recommended dose, and third, albeit with less published results, to consider the combination of both drugs. We considered all three options and, in order to interpret more correctly the results, we randomised the patients to any of the three therapies.

A more effective BP control and a further drop in proteinuria can be obtained with titration of the ACE-I dose.³⁰ However, some evidence indicates that the antiproteinuric capacity of ACE-I, which is

Table 2 Percentage of subjects achieving adequate blood pressure control after treatment (<140/90 mmHg)

| | Benazepril (%) (n=12) | Valsartan (%) (n=12) | Combination (%) (n=12) |
|---------|--------------------------|-------------------------|---------------------------|
| Month 3 | 33.3 | 50.0 | 33.3 |
| Month 6 | 50.0 | 66.7 | 58.3 |

Data are expressed in percentage of patients

the best reno-protective indicator of the drug, could be dose-independent.^{31,32} On the other hand, in the presence of a diminished glomerular filtration rate, dose titration of the majority of ACE-I is accompanied by drug accumulation, due to diminished renal excretion.^{33,34} Our results show that recommended dose titration of benazepril according to renal function levels is not accompanied by a further reduction of proteinuria, although BP fell significantly with the ACE-I plus other medications.

Most of the known physiological and pharmacological actions of Ang II, including its cardiovascular, central nervous system and renal actions,¹³ are mediated by stimulation of AT₁-receptors. RAS blockade could be more complete after the administration of an ARB, compared with an ACE-I.¹⁴ Nevertheless, ARBs + ACE-I have demonstrated similar effects on reduction of microalbuminuria and proteinuria, both in animals³⁵⁻³⁸ and humans,¹⁵⁻¹⁸ and a similar effect on renal function protection in animal models.^{39,40} There are few studies on benefits of titration of an ARB on proteinuria; preliminary data seem to be positive, in particular when doses well above the recommended dose range are used.⁴¹⁻⁴³ Moreover, dose titration of valsartan is not accompanied by drug accumulation, even in the presence of end-stage renal disease,⁴¹ nor by a higher incidence of side-effects.⁴² Our results show that valsartan titration within the recommended dose range exhibits a trend for a supplementary decrease of proteinuria in patients previously treated with an ACE-I. This effect could be the consequence of a more effective blockade of the RAS.⁴⁴⁻⁴⁵ However, the benefits of valsartan could also be due to the consequence of counteracting the 'ACE-escape' which has been described during chronic therapy with ACE-I.^{11,12}

The combination of an ACE-I and an ARB could be of benefit for the kidney.^{22,43} This possibility is based on the concept that these are different classes of agents, acting through different mechanisms of action and that their combination could implement the degree of blockade of Ang II. In fact, data obtained in animal models⁴⁶ have shown a synergistic effect with the combined administration of an ACE-I and an ARB. In humans, the combination of the two classes of drugs has been shown to be safe for renal function and unwanted side-effects, in particular hyperkalaemia.²² Indeed, some data indicate that combination therapy could further reduce high BP levels,²³⁻²⁶ decrease proteinuria^{27,28} and improve the clinical status of

Table 3 Evolution of natriuresis, serum potassium and creatinine clearance in follow-up, showing no significant differences between groups

| Therapy | | Basal | 7 days | 1 month | 3 months | 6 months |
|-------------------------------------|----------------------------------|---------|---------|---------|----------|----------|
| Benazepril (n=12) | Natriuresis (mmol/24-hour) | 176±66 | 206±96 | 209±75 | 201±66 | 196±78 |
| | Serum potassium (mmol/L) | 4.6±0.7 | 4.4±0.6 | 4.3±0.7 | 4.5±0.6 | 4.5±0.6 |
| | Creatinine clearance (ml/minute) | 71±25 | 78±39 | 83±34 | 75±34 | 71±28 |
| Valsartan (n=12) | Natriuresis (mmol/24-hour) | 165±56 | 180±86 | 199±65 | 178±54 | 191±65 |
| | Serum potassium (mmol/L) | 4.3±0.4 | 4.7±0.6 | 4.4±0.4 | 4.7±0.6 | 4.6±0.5 |
| | Creatinine clearance (ml/minute) | 68±23 | 72±30 | 77±28 | 72±25 | 70±23 |
| Valsartan + benazepril (n=12) | Natriuresis (mmol/24-hour) | 180±61 | 198±77 | 172±62 | 190±62 | 192±67 |
| | Serum potassium (mmol/L) | 4.5±0.7 | 4.6±0.4 | 4.6±0.6 | 4.8±0.4 | 4.6±0.7 |
| | Creatinine clearance (ml/minute) | 66±24 | 71±31 | 74±24 | 75±31 | 69±21 |

patients with heart failure.^{47,48} Our results indicate that patients receiving combined therapy with ARB-ACE-I will benefit more than those receiving any of the two monotherapies titrated to the maximal recommended doses. These results were obtained with a similar degree of BP control between groups and in the presence of stable glomerular filtration rate values. This indicates that the changes in proteinuria were secondary to variations in intrarenal haemodynamics independent of systemic BP and the amount of protein filtered.

In conclusion, the administration of benazepril according to renal function and the addition of other (non-ACE-I/non-ARB) therapies to obtain BP and proteinuria control did not induce any significant change in proteinuria. The titration of valsartan facilitated a further decrease in protein excretion that almost attained statistical significance. New clinical trials are required to demonstrate the possible benefits of ARB titration.

The administration of the combination of benazepril and valsartan obtained a significant decrease in this parameter.

The results of this pilot study show that the best effects on BP and proteinuria control are obtained with the ACE-I-ARB combination. However, titration of valsartan could also be of value.

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