Effect of strict blood pressure control on proteinuria in renal patients treated with different antihypertensive drugs

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Abstract

**Background.** The severity of proteinuria is the main predictive factor in the progression of renal failure in chronic nephropathies. Therefore, action aimed at reducing proteinuria should be a priority in the treatment of these patients. Various antihypertensive drugs, in particular the angiotensin-converting enzyme inhibitors (ACEIs), have a greater antiproteinuric effect, although it is difficult to establish whether this is due only to their effect on arterial blood pressure (BP) or to other mechanisms associated with blockade of the renin-angiotensin system (RAS).

**Methods.** The evolution of proteinuria after two successive treatment periods was studied prospectively for 2 years in 22 patients with chronic glomerulonephritis. In period I, which lasted for 12 months, BP was strictly controlled (<125/75 mmHg) and the patients received random and double-blind treatment with a β-blocker (βB), atenolol; a non-dihydropyridine calcium channel blocker (CCB), verapamil; an ACEI, trandolapril; or a fixed combination of the latter two. In period II, all of the patients received treatment openly for an additional 12 months with a fixed combination of verapamil + trandolapril at half the dose of the preceding period, to obtain conventional control of BP at <140/90 mmHg.

**Results.** The mean level for basal SBP/DBP was 136 ± 14.86 ± 7 mmHg, which decreased in period I to 121 ± 15/76 ± 8 mmHg (P = 0.01) and to 124 ± 5/78 ± 8 mmHg (P < 0.05) at 6 and 12 months of treatment, respectively. There were no differences in the BP reached in the four therapy groups; however, proteinuria only decreased in the patients treated with trandolapril alone or in combination with verapamil. In period II, BP levels rose to 134 ± 10/84 ± 8 mmHg (P < 0.05); this increase in BP was accompanied by an increase in proteinuria in those patients who had received the ACEI alone or in combination in the previous period, while in patients previously treated with a βB or a CCB, proteinuria decreased, in spite of the increase in BP.

**Conclusions.** With equal BP control, treatment with the ACEI trandolapril alone, or in combination with a CCB, has a greater antiproteinuric effect than that obtained with other antihypertensive drugs, but this effect is attenuated if BP is not strictly controlled.

**Keywords:** angiotensin-converting enzyme inhibitors (ACEIs); blood pressure control; chronic glomerulonephritis; chronic non-diabetic nephropathies; proteinuria; renal disease

Introduction

Since the publication of the Modification of Diet in Renal Diseases Study (MDRD) [1,2], we know that strict control of BP below 125/75 mmHg slows the progression to end-stage renal disease (ESRD) in patients with nephropathy and proteinuria >1 g/day. However, although some antihypertensive drugs, specifically the angiotensin-converting enzyme inhibitors (ACEIs), have a greater antiproteinuric and renoprotective effect, it is not clear whether this effect is due only to BP control or to another mechanism independent of the antihypertensive action. The majority of studies show greater benefits from treatment with ACEIs. In 1997, Giatras [3] published a meta-analysis which studied the effect of the ACEIs on the evolution of non-diabetic primary nephropathies compared with other antihypertensive drugs, and concluded that the ACEIs are more effective than other antihypertensive agents in preventing the risk of development of ESRD, although in this study the beneficial effect of the ACEIs on the progression of renal disease coincides with better BP control. Later, the Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN) [4,5] showed in the REIN study that the ACEI ramipril decreases proteinuria and reduces the fall in
glomerular filtration rate in patients with nephropathy and proteinuria $> 3 \, \text{g/day}$ and that this slowing of the progression rate of ESRD correlates with the decrease in proteinuria but not with the degree of control of systolic BP.

Here we analyse the effect of different antihypertensive drugs on proteinuria in primary nephropathies: $\beta$-blockers ($\beta$Bs), ACEIs, non-dihydropyridinic calcium channel blockers (CCBs), and the fixed combination of the latter two, in relation to BP control.

**Subjects and methods**

The patients were recruited from the out-patient clinic of the Division of Nephrology at our hospital and the first stage of the study was part of a clinical multicentre study in which another 11 Spanish hospitals participated [6]. Patients were eligible for the study if they had primary renal disease with normal renal function or modest chronic renal failure defined as a creatinine clearance of $> 50 \, \text{ml/min}$ and proteinuria $> 2 \, \text{g/day}$. Patients were 18–70 years old, had no diabetes or systemic diseases, and no need for immunosuppressive agents, steroids or non-steroidal anti-inflammatory drugs. Patients could be hypertensive or not [7]. Those patients whose BP was $>140/90 \, \text{mmHg}$ or who received antihypertensive treatment were considered hypertensive. Patients with complete AV blockade, a wide PR interval, or an RS wave in their ECG were excluded from the study.

The study was approved by the local medical ethics committee and written informed consent was obtained from each patient.

**Study protocol**

All patients were prescribed a sodium-restricted diet and protein intake was advised to be kept at 1–1.5 $\, \text{g/kg body weight per day}$.

**Period I (strict control of BP).** Four weeks prior to the beginning of the study, antihypertensive drugs (if used) were withdrawn and the patients entered into a run-in period with a placebo. Thereafter, they were randomized to receive either atenolol at 50 mg per day, verapamil at 240 mg per day, trandolapril at 2 mg per day or the fixed combination of 180 mg of verapamil plus 2 mg per day trandolapril in a double-blind fashion at a ratio of 1:1:1:1. After 4 weeks of active treatment, all drugs were titrated by doubling the medication as follows: atenolol, 2×50 mg/day; verapamil, 2×240 mg/day; trandolapril, 2×2 mg/day; and the fixed combination of verapamil plus trandolapril, 2×(180+2) mg/day.

Patients were followed for 48 weeks on this treatment. At the eighth week of active treatment, the medication was reduced by half in cases of poor tolerance to high strength medication and furosemide was added in the event of poor BP control. The active treatment and placebo were supplied by Knoll AG Spain.

**Period II (conventional BP control).** At the end of period I, all patients received open treatment with a fixed combination of verapamil plus trandolapril (180+2 mg/day) for another 12 months, as this was considered the best antiproteinuric therapeutic option after the double-blind treatment.

In both periods, during each visit, blood pressure, heart rate and body weight were recorded. Blood was withdrawn for measurement of electrolytes, creatinine and urea, and 24-h urine was collected for evaluation of sodium, potassium, creatinine, urea and protein excretion using standard laboratory techniques. Creatinine clearance and the protein/creatinine ratio in urine was measured.

**Statistical analysis**

Results are presented as mean ± SD. The level of significance was taken as $P<0.05$. Comparisons between groups were made using Student’s $t$-test for paired or unpaired samples. Linear association between the decrease in BP and decrease in proteinuria was studied by Pearson’s correlation.

**Results**

**Patients**

Overall, 22 patients were included in the study. Nineteen were male and three were female, between the ages of 26 and 58 (mean: 42 ± 11 years). As a group, the patients had a relatively well-preserved renal function, mildly elevated or normal blood pressure and heavy proteinuria: creatinine clearance was $97 ± 31 \, \text{ml/min}$, serum creatinine was $1.3 ± 0.4 \, \text{mg/dl}$ and the protein/creatinine ratio in urine was $2.8 ± 1.4$ (nephrotic range $> 2$).

Nine of the patients were previously hypertensive. Mean BP in the total group of patients was $136 ± 14/86 ± 8 \, \text{mmHg}$ at the end of the placebo treatment period.

All of the patients were diagnosed with chronic glomerulonephritis (GN): there were six cases of mesangial IgA GN, two of mesangial GN without IgA, six with focal and segmental sclerosis, one membranoproliferative GN and seven non-biopsied GN.

In period I, five patients received treatment with atenolol, seven with verapamil, six with trandolapril and four with a fixed combination of trandolapril plus verapamil. Age, sex distribution, baseline blood pressure, renal function and proteinuria were not different among the four treatment groups.

**Blood pressure**

In period I, BP decreased significantly from the baseline to 6 and 12 months in the total group from $136 ± 14/86 ± 7$ to $121 ± 15/76 ± 7 \, \text{mmHg}$ ($P=0.01$) and $124 ± 16/18 ± 8 \, \text{mmHg}$ ($P<0.05$), respectively, and no differences were found between the four treatment groups at any time during the follow-up period (Figure 1).

**Proteinuria (Figure 2)**

The protein/creatinine ratio in urine (Pr/Cr) showed no change throughout the first study period (strict BP control) in the total patient group: $2.8 ± 1.4$ basal vs $2.4 ± 2$ at the end of 12 months of treatment.
Fig. 1. Evolution of BP throughout the two periods. Period I, strict BP control with four treatment possibilities: \( \beta \)B, CCB, ACEI or a fixed combination of ACEI + CCB. Period II: all the patients were treated with a combination of ACEI + CCB at half the dose of the preceding period. The four groups were homogeneous regarding the BP reached.

The ratio only decreased significantly in the patients who received the ACEI trandolapril, alone or in combination with verapamil (\( n = 10; \ 2.9 \pm 1.6 \) to 1.7 ± 1.1; \( P < 0.05 \)), and did not vary in the patients treated with atenolol or verapamil, despite similar BP control.

In period II (conventional BP control), the Pr/Cr ratio again did not change in relation to the previous period in the total patient group (from 2.4 ± 2 to 2.7 ± 2), but in the patients treated with trandolapril alone or in combination in period I, proteinuria increased (Pr/Cr of 1.7 ± 1 to 3.4 ± 2.0, \( P < 0.05 \)), while in the rest the introduction of the ACEI was accompanied by a reduction in proteinuria (Pr/Cr of 2.7 ± 1.7 to 1.7 ± 1, \( P = 0.03 \)). The increase in SBP in both groups of patients was similar: 11 ± 4 and 10 ± 5 mmHg, respectively.

We found no correlation between the decrease in proteinuria and the decrease in BP levels in patients treated with trandolapril in both periods, which suggests that the antiproteinuric effect of trandolapril is related not only to its action on BP.

**Renal function**

Neither serum creatinine nor creatinine clearance changed throughout the study in the total patient group, nor in any of the therapeutic groups. Only one patient, who was treated with atenolol, doubled blood creatinine levels in the 12-month period I treatment.

Blood creatinine remained at 1.5 ± 0.4 at the end of period II in the total patient group, with no variation with respect to period I (1.4 ± 0.7 mg/dl) or to baseline at the beginning of the study (1.34 ± 0.4 mg/dl).

**Discussion**

Independent of the nature of the initial lesion, in nephropathies with proteinuria the rate of protein
excretion in urine is the most powerful predictor of the progression of the renal disease [2,8,9]. These patients with high proteinuria are the ones who benefit most from a treatment capable of reducing the transglomerular traffic of proteins and consequent prevention of renal toxicity [10]. Therefore, protein-restricted diets and the reduction of systolic and glomerular BP [11] have been the fundamental basis of treatment for these patients [2].

What is the best choice of antihypertensive medication in these patients with renal disease and proteinuria? Although some authors have not observed treatment with ACEIs to be more beneficial [12], the specific renal vasodilator effect and the decrease in glomerular pressure they produce make, in theory, the ACEIs more efficient in decreasing proteinuria and slowing down the progression to ESRD, as has been observed in patients with diabetic nephropathy [13]. Giatras’ meta-analysis [3] clearly shows a more favourable effect of the ACEIs in reducing the risk of developing ESRD, later confirmed by the REIN study [4], which demonstrates that treatment of these patients with ramipril decreases the urine protein excretion rate more than would be expected in relation to the degree of BP reduction. According to our data, strict control of BP only reduces proteinuria in patients treated with ACEIs, and the decrease in proteinuria does not correlate with the decrease in BP, which suggests that this antiproteinuric effect is at least not only dependent on the antihypertensive action.

The renoprotective effects of the CCBs are more debatable. The dihydropyridinic CCBs, in particular nifedipin, seem to have an adverse effect on glomerular permeability [5,14,15]. There are few data available regarding the antiproteinuric effect of non-dihydropyridinic CCBs when administered alone. Bakris showed a beneficial additive effect of the combination of ACEI + verapamil on proteinuria in diabetic nephropathy [16]. However, in our patients, verapamil alone did not modify proteinuria despite strict BP control, although it is efficient if administered in combination with an ACEI.

An especially relevant finding in our study is that in the patients treated with an ACEI, if BP control worsened, even at levels of 140/90 mmHg, proteinuria increased, which means that strict BP control is necessary to maximize the antiproteinuric effect of the ACEI. This stricter control of BP in patients with nephropathies makes recourse to a combination of drugs necessary in a high percentage of these cases, as shown in the HOT study [17]. Therefore, the combination of an ACEI and a CCB seems to be an appropriate therapeutic option.

In conclusion, the ACEIs are a better therapeutic option in patients with primary nephropathies and proteinuria with respect to BP control and the decrease in urinary protein excretion; however, to optimize this antiproteinuric effect, BP must be strictly controlled. This may require the combination of various drugs, and our experience has shown the combination of an ACEI and a CCB to be useful.

References