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Angiotensin converting enzyme inhibitors for reduction of proteinuria in children with steroid-resistant nephrotic syndrome

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Abstract. The effects of angiotensin converting enzyme inhibitors (ACEI) on proteinuria, renal function, and serum proteins were evaluated in six children with steroid-resistant nephrotic syndrome and proteinuria of 3–15 g/24 h (277 ± 47 mg/m^2 per hour). Following ACEI, proteinuria decreased from 7,408 ± 2,385 (mean ± SEM) to 3,746 ± 1,395 mg/24 h (P <0.05). Creatinine clearance was 87.8 ± 22.6 before and 96.4 ± 23.6 ml/min per 1.73 m^2 after ACEI. In two patients, inulin and para-aminohippuric acid clearances were normal before and after ACEI, together with parallel reductions of urine protein of 50% and 46%. Clearance of total protein was reduced by 56% following ACEI, compared with reduction in the clearance of gamma globulin by 58% and albumin by 39.5%. No significant change was seen in blood pressure, serum albumin, or total protein following ACEI. After ACEI, diuretic doses were able to be reduced or eliminated in three patients. Reduction of proteinuria was sustained during a followup period of 11–20 months in three patients. ACEI may be of benefit in the clinical management of children with steroid-resistant nephrotic syndromes, allowing reduction in diuretic requirements.

Key words: Proteinuria – Nephrotic syndrome – Angiotensin converting enzyme inhibitors – Renal function

Introduction

Proteinuria in the nephrotic range (>40 mg/m^2 per hour) results in hypoalbuminemia, hyperlipidemia, edema, ascites, hypogammaglobulinemia, defects in cellular immunity, a predisposition to infections including peritonitis, a hypercoagulable state, and negative nitrogen balance [1]. The magnitude of proteinuria appears to constitute a risk factor for progression of renal disease [2–6]. Thus, there are compelling reasons to reduce proteinuria in nephrotic patients who are resistant to standard therapy such as corticosteroids or cytotoxic agents.

A reduction in proteinuria following pharmacological angiotensin converting enzyme inhibition has been documented in animal models, and observed in adult patients receiving angiotensin converting enzyme inhibitors (ACEI) for treatment of hypertension [7, 8], in diabetic patients with proteinuria [8–10], and more recently in adults with other renal diseases [11]. However, there has been concern regarding potential adverse effects on renal function [12]. In a single published study of eight children receiving captopril [13], urine protein excretion, as reflected by protein/creatinine ratios, was reduced by 60%–70%. Renal function, as estimated by the formula of Schwartz et al. [14], did not change.

The purpose of our study was to assess the clinical and laboratory response, including measured renal function, to ACEI therapy in children with steroid-resistant, nephrotic proteinuria.

Methods

Six children were studied (Table 1). All had urinary protein excretion in excess of 100 mg/m^2 per hour. Renal diagnoses were documented by biopsy: four children had focal segmental glomerulosclerosis (FSGS), one chronic Henoch-Schönlein purpura (HSP) nephritis, and in one light microscopy suggested minimal-change lesions but immunofluorescence showed mesangial IgA deposition. This child had nephrotic syndrome without hematuria. Five patients had failed to respond to corticosteroids. Three patients received prednisone 60 mg/m^2 per day for 8–12 weeks, one had a biopsy after 60 mg/m^2 per day for 4 weeks, and one received 53 mg/m^2 per day (90 mg) for 6 weeks. Patient no. 4 (HSP) received 40 mg/m^2 per day for 12 weeks, and appeared to respond to prednisone initially, but heavy proteinuria subsequently recurred. Three children received and failed to respond to cyclophosphamide.

Enalapril, started at a low dose and increased as tolerated to 10 mg daily (in two doses), was used in five patients. Patient no. 4 received captopril at 37.5 mg daily (in three doses). Short-term studies of the effect of ACEI were performed 2–8 weeks following initiation of therapy in five patients, and in one patient (patient no. 6) 2 days after starting

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Table 1. Patient characteristics

Patient no.	Age	Disease	Serum creat (mg/dl)	Serum TP (g/dl)	Serum Alb (g/dl)	Serum Chol (mg/dl)
1	12 months	FSGS	0.5	3.7	1.6	447
2	15 months	FSGS	0.5	4.3	2.0	542
3	11 years 8 months	FSGS	0.7	3.8	1.7	436
4	9 years 1 month	HSP	0.7	5.3	3.3	NA
5	2 years 3 months	FSGS	0.4	3.9	1.7	734
6	11 years 6 months	MCL/IgA	0.9	4.6	2.2	1,122

FSGS, Focal segmental glomerulosclerosis; HSP, Henoch-Schönlein purpura; MCL, minimal-change lesions; creat, creatinine; TP, total protein; Alb, albumin; Chol, cholesterol; NA, not available

the medication. All patients were on a sodium-restricted diet with no changes in dietary protein intake throughout the study.

Biochemical parameters, including serum creatinine, serum albumin, total protein, and cholesterol, were measured by standard laboratory methods. Analysis of serum and urinary proteins by electrophoresis was also performed. Baseline urinary excretion of protein was assessed by a timed 12- to 24-h urine collection, and timed collections were used whenever possible in subsequent assessments. In some younger patients, urinary total protein/creatinine ratios (both timed and random) were used during followup evaluations. Urinary protein was measured by the Coomassie blue dye exclusion technique. Renal function was assessed by 12- to 24-h creatinine clearances. In two patients, inulin and para-aminohippuric acid (PAH) clearances were performed before and after administration of ACEI, using methods previously described [15].

Results

Following ACEI administration, urinary total protein decreased by a mean of 52.4% ($P < 0.05$, paired t-test) and urine total protein/creatinine ratio by a mean of 54.4% ($0.05 < P < 0.10$, Table 2). The reversibility of this effect was evident in two patients in whom interruption of ACEI was followed by increases in urine protein of 208% and 345%. With resumption of ACEI, proteinuria again decreased. Total protein clearances, calculated in three patients, were 0.27, 0.28, and 0.28 ml/min per 1.73 m^2 before ACEI and 0.049, 0.125, and 0.115 ml/min per 1.73 m^2, after ACEI, decreasing by a mean of 65% from baseline values. In one patient in whom inulin and PAH clearances were measured, we evaluated the effect of ACEI on clearance of albumin compared with total protein and gamma globulin (Fig. 1).

Creatinine clearances measured before and after ACEI are shown in Table 2, and standard clearances of PAH and inulin in Fig. 2. With no significant change in inulin clearance, urine protein excretion was reduced by 50% and 46% following ACEI. Because of increases in PAH clearance, the filtration fraction decreased from 13% to 8.7% in one patient, and from 17% to 15% in the other.

Following ACEI, diuretic requirements were reduced. Patient no. 1 who had required large doses of furosemide, hydrochlorothiazide, spironolactone (Aldactone), and intravenous albumin needed no diuretics or albumin after ACEI. In patient no. 2 diuretics were reduced from furosemide and hydrochlorothiazide in divided daily dose to furosemide every other day, and in patient no. 6 from furosemide, metolazone, and Aldactone to a lower dose of furosemide only. The remaining three patients did not require diuretics before or after ACEI. There was no significant change in representative blood pressures, serum total protein or albumin after ACEI in the group as a whole (Table 2).

Reduction of proteinuria was sustained in three patients with FSGS followed for 11, 17, and 20 months on ACEI therapy. Serum creatinine measurements at the last observation were 0.3–0.6 mg/dl. In two patients (1 FSGS, 1 HSP) followed for 17 and 6 months, respectively, reduction of proteinuria appeared to be sustained, but urine protein values may have been influenced by other variables. In

Table 2. Response to angiotensin converting enzyme inhibitors (ACEI)

Patient no.	Urine TP (mg/24 h)			Urine TP/creatinine ratio (mg/mg)			Clearance creat (ml/min per 1.73 m^2)		Blood pressure (mm Hg)		Serum TP (g/dl)		Serum Alb (g/dl)	
	Before	ACEI	% change	Before	ACEI	% change	Before	ACEI	Before	ACEI	Before	ACEI	Before	ACEI
1	3,778	973	–74	41.5	8.2	–80	48	43	105/60	100/65	3.7	5.0	1.6	2.3
2	4,180	NA	NA	57.4	9.7	–83	38	42	140/90	118/52	4.3	4.1	2.0	1.5
3	10,203	5,107	–50	11.52	7.3	–37	138	125	112/76	104/76	3.8	4.4	1.7	2.0
4	3,215	1,576	–51	4.94	NA	NA	91	NA	120/78	110/68	5.3	4.8	3.3	2.3
5	4,495	2,622	–42	19.9	11.4	–43	143	113	104/58	106/52	3.9	4.5	1.7	1.5
6	15,350	8,452	–45	16.2	11.6	–29	72	159	110/90	130/80	4.6	NA	2.2	NA
Mean[a]	7,408	3,746	–52.4	29.3	9.64	–54.4	88	96	115/75	111/65.5	4.2	4.6	2.1	1.9
SEM	2,385	1,395	5.7	8.8	0.86	11.4	4.3	24	47/5.69	4.49/4.80	0.30	0.16	0.32	0.18
P[b]		<0.05			NS			NS		NS		NS		NS

SEM, Standard error of mean; NS, not significant

[a] Excluding patients with incomplete data

[b] Paired t-test

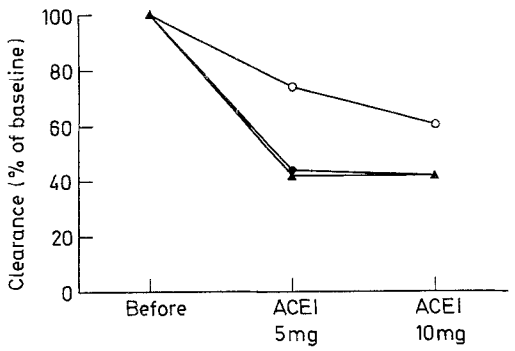

Fig. 1. Clearance of the large molecular weight molecules gamma globulin (—▲—, mol.wt. >140 kDa), and total protein (—●—, mol.wt. 340 kDa) and albumin —○—, mol.wt. 40–69 kDa) in one patient studied on two doses of the angiotensin converting enzyme inhibitor (*ACEI*) enalapril

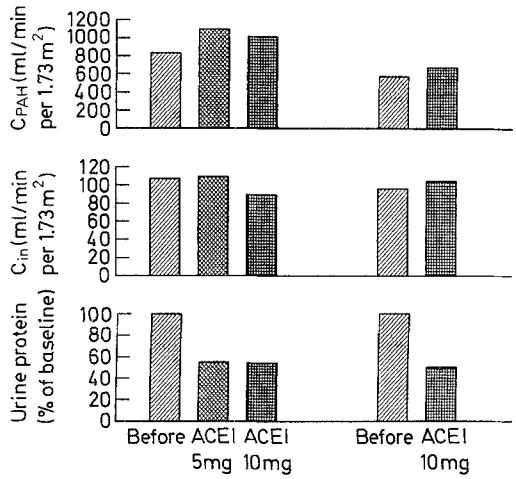

Fig. 2. Inulin (C_{in}) and para-aminohippuric acid (C_{PAH}) clearances and urine protein excretion (expressed as % of pre-ACEI baseline protein excretion) in two patients before and after ACEI. One patient was studied on 5 mg and 10 mg of enalapril daily, the other while on 10 mg daily

patient no. 6 ACEI were discontinued after 2 months because of an increase in serum creatinine. ACEI were well tolerated. None of the patients had hypotension; mild hyperkalemia in one patient resulted in changes in the enalapril dose.

Discussion

Our data confirm that ACEI are effective in reducing proteinuria in children with steroid-resistant nephropathies. The children in our study had much heavier proteinuria (urinary total protein/creatinine ratio 25.2 ± 8.2 and urine protein excretion 277 ± 47 mg/m^2 per hour) than those reported by Trachtman and Gauthier [13] (urinary total protein/creatinine ratio 2.8 ± 1.3 and urine protein excretion 60.4 ± 21.3 mg/m^2 per hour), yet the effects of ACEI were similar. The substantial reduction in proteinuria occurred without compromise of glomerular filtration rate as measured by creatinine and inulin clearances, and was sustained during up to 20 months of followup.

ACEI-induced reductions in proteinuria could be due to a decrease in the glomerular capillary plasma flow rate, a decrease in transcapillary hydraulic pressure, or to a change in permeability properties of the glomerular capillary wall. A selective decrease in intraglomerular transcapillary pressure, independent of systemic blood pressure and due to ACEI-mediated efferent arteriolar dilatation, is supported by a large body of evidence [12, 16–20]. ACEI have also been shown to influence the size selective properties of the glomerular basement membrane [17]. Although preliminary, our data showing greater reductions in clearance of the larger molecular weight gamma globulin and total protein compared with albumin (Fig. 1) support a role for such ACEI-induced changes in humans [21].

Angiotensin II (AII) is known to stimulate sodium, bicarbonate, and water reabsorption in proximal convoluted tubules [22–24]. Angiotensin I, angiotensin converting enzyme, and AII are all found in the renal proximal tubule [25, 26], and the amount of angiotensin converting enzyme in the kidney increases progressively with proteinuria in a rat model of nephrosis [27]. Thus, inhibition of AII production in proximal tubules of patients with heavy proteinuria might ameliorate the sodium retention of proteinuric states. Such a mechanism could help to explain the much reduced diuretic requirements of our patients, even though serum albumin and total protein did not change following ACEI.

The use of ACEI may have practical implications for clinical management of children with steroid-resistant nephrotic syndromes. Our patients showed reductions in edema, ascites, and diuretic requirements. Before ACEI the smaller children in the study were losing protein at 0.33–0.38 g/kg body weight daily. With less protein lost in the urine after ACEI, negative nitrogen balance should be less of a concern. Experience with larger numbers of nephrotic children is needed to confirm these observations. ACEI were well tolerated by nephrotic children, although the possibility of a decline in glomerular filtration rate must always be borne in mind as clinical circumstances change [12], and prudence would dictate that they not be initiated during marked intravascular volume depletion.

Data from numerous animal studies suggest that glomerular hypertension and hyperfiltration contribute to progression of renal insufficiency [12, 16, 19, 20, 28], and that ACEI amelioration of these hemodynamic changes protects against the development of glomerulosclerosis [12, 16, 17, 20, 28]. Although the significance of glomerular hypertension and hyperfiltration in human nephropathies remains to be unequivocally established, present evidence suggests that it plays an important role [12, 29, 30]. Thus, a favorable effect on the rate of progression of renal disease should not be overlooked as a potential long-term benefit of the use of these agents in children with steroid-resistant nephrotic syndromes. Preliminary clinical data suggest that ACEI may indeed slow the rate of progression of FSGS and other nephropathies [31, 32]. Long-term trials are needed to address this issue.

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