Effectiveness and Safety of the Angiotensin II Antagonist Irbesartan in Children With Chronic Kidney Diseases

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Background: Studies in adults with chronic kidney diseases demonstrate that the orally available angiotensin II antagonist irbesartan reduces arterial pressure and pathological proteinuria, mostly with an excellent tolerability profile. Little information is available on irbesartan in childhood.

Methods: A total of 44 pediatric outpatients with chronic kidney disease (27 male and 17, aged 3.7 to 18 years, median 10 years) were given irbesartan once a day during 18 weeks for arterial hypertension ($N = 23$), proteinuria ($N = 8$), or both ($N = 13$).

Results: In patients with hypertension, the use of irbesartan 4.1 (3.1–5.3) mg/kg body weight daily (median and interquartile range) was associated with a decrease ($P < .005$) in arterial pressure by 17 (13–22)/10 (7–12) mm Hg. In patients with overt proteinuria the urinary protein excretion decreased ($P < .01$) during treatment with irbesartan (2.9 [2.0–4.8] mg/kg body weight) by 52 (0–75) mg/[$m^2 \times$ h]), whereas plasma albumin increased ($P < .05$) by 4 (1–5) g/L. The frequency of abdominal pain, constipation, cough, diarrhea, dizziness, edema, fatigue, headache, insomnia, myalgia, orthostasis, and rash was similar before and with irbesartan. Plasma sodium slightly decreased, whereas plasma potassium increased, with irbesartan ($P < .01$).

Conclusions: In pediatric patients with chronic kidney diseases, irbesartan given once a day for 18 weeks significantly reduces arterial pressure and proteinuria, with an excellent tolerability and side effect profile. Am J Hypertens 2002;15:1057–1063 © 2002 American Journal of Hypertension, Ltd.

Key Words: Irbesartan, chronic kidney disease, hypertension, proteinuria, childhood.

Angiotensin II receptor blockers, subsequently referred to as angiotensin antagonists, represent a class of drugs that inhibit the renin-angiotensin II–aldosterone system by blocking angiotensin II type 1 receptor.[1] A number of studies have demonstrated the efficacy of the angiotensin antagonist irbesartan given once a day in the treatment of hypertension. As an antihypertensive agent, irbesartan is as effective as converting enzyme inhibitors, thiazide diuretics, β-blockers, and calcium channel blockers, mostly with a better tolerability profile, and at least as effective as currently available angiotensin antagonists such losartan, valsartan, and candesartan.[2] As with other angiotensin antagonists, the efficacy of irbesartan is enhanced by concomitant administration of a diuretic. In combination with other classes of drugs such as calcium channel blockers or β-blockers, irbesartan is also efficacious in the treatment of moderate to severe arterial hypertension.[2] Finally, studies in patients with chronic kidney diseases have shown that irbesartan reduces pathologic proteinuria and mitigates the disease progression.[3–5]

Antihypertensive drugs are not usually investigated in children before approval for marketing in adulthood, and information is mostly acquired during clinical use, with initial doses established by extrapolations from doses in adults.[6] The purpose of the present report is to describe the experience with the angiotensin antagonist irbesartan given for 18 weeks in 44 pediatric outpatients with chronic kidney diseases.

Patients and Methods

Arterial Hypertension

Thirty-six pediatric outpatients (22 male and 14 female, aged 3.7 to 18 years, median 10 years) with arterial hy-

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pertension were prospectively evaluated in Berne and Milan between 1999 and 2001. The underlying renal conditions were glomerular diseases ($N = 13$), urinary tract malformations ($N = 12$), polycystic kidney disease ($N = 3$), nephronophthisis ($N = 1$), renal artery stenosis ($N = 1$), and renal transplant ($N = 6$). Renal function[7] was normal (normal plasma creatinine for age and sex, $N = 16$), mildly reduced (plasma creatinine increased but <177 μmol/L; $N = 8$) or moderately reduced (plasma creatinine 178 to 354 μmol/L, $N = 7$). Five patients were on regular dialysis (hemodialysis, $N = 1$; home peritoneal dialysis, $N = 4$). In the patients, sitting arterial pressure was persistently above the centile 95 for age, body length, and sex.[8] Of the 36 patients, 12 subsequently referred to as "pretreated" were on medication with a variety of antihypertensive agents (diuretics, $N = 5$; diuretics associated with amlodipine, $N = 3$; amlodipine, $N = 2$; atenolol, $N = 2$). The regularly scheduled antihypertensive regimen had not been changed for at least 6 weeks and was not modified during treatment with irbesartan. The remaining 24 patients, subsequently referred to as "unpretreated," were not on antihypertensive drugs. Before irbesartan administration, arterial hypertension was either mild (systolic value $\leq$19 mm Hg or diastolic value $\leq$9 mm Hg above centile 95, $N = 8$), moderate (systolic value 20 to 39 mm Hg or diastolic value 10 to 19 mm Hg above centile 95, $N = 11$), or severe (systolic value $>$39 mm Hg or diastolic value 19 mm Hg above centile 95, $N = 17$).[9] Irbesartan was delivered once a day by commercially available tablets (75, 150, and 300 mg), starting with a dose of 37.5 (body weight ranging 10 to 20 kg), 75 (body weight 21 to 40 kg), or 150 mg (body weight $>$40 kg) on awakening.[9] The dose of irbesartan was doubled if there was failure to decrease systolic arterial pressure $\leq$10 mm Hg 3 to 5 weeks after starting irbesartan, or if systolic arterial pressure was above the centile 95 for body length and sex 8 to 12 weeks after starting irbesartan. Arterial pressure, heart rate, and body weight were measured, and blood was taken for the determination of packed cell volume (microhematocrit centrifuge), sodium and potassium (ion selective electrodes), creatinine (kinetic alkaline picrate assay), uric acid (allantoin-uricase assay), albumin (bromcresol purple assay), and aminotranferases and creatine kinase (kinetic assays) from each patient before entering the trial and after 18 weeks of irbesartan. The whole blood cyclosporine trough level was measured using a specific monoclonal fluorescent polarization immunoassay in the patients treated with this agent. Patients were monitored by a written questionnaire before and during irbesartan treatment for the presence of abdominal pain, constipation, cough, diarrhea, dizziness, edema, fatigue, headache, insomnia, myalgia, nausea, orthostasis, and rash. Sitting ($>$10 min) arterial pressure (first and fifth Korotkoff sounds) was measured after overnight by means of a mercury sphygmomanometer with a cuff covering approximately three quarters of the upper arm length from the acromion to the olecranon; each recorded value was the mean of at least three consecutive measurements. The effect of irbesartan on arterial pressure was evaluated 24 h postdose.

Overt Proteinuria

Twenty-one outpatients (12 male and 9 female subjects, aged between 4.8 and 14, median 10 years) with overt proteinuria, defined as urinary protein excretion $>$6 mg/[$m^2 \times$ h], were prospectively evaluated. They were 13 of the aforementioned patients with arterial hypertension (glomerular diseases, $N = 12$; nephronophthisis, $N = 1$; see Arterial Hypertension) and eight normotensive patients (five male and three female subjects, aged 4.1 to 14 years, median 12 years) with chronic glomerular diseases. Renal function was either normal ($N = 16$) or mildly reduced ($N = 5$).

Irbesartan was given at a once-a-day dose of 37.5 (body weight ranging between 10 and 20 kg), 75 (body weight between 20 and 40 kg) or 150 mg (body weight $>$40 kg) on awakening during 18 weeks. In the eight normotensive patients with pathologic proteinuria, the dose of irbesartan was not further increased during the study. Arterial pressure, heart rate, body weight, laboratory values, and the written questionnaire were evaluated as in patients with arterial hypertension. In addition, every patient carried out a timed overnight urine collection during 3 consecutive days both before and with irbesartan for determination of total protein (Coomassie blue assay) and creatinine (kinetic alkaline picrate assay). The urinary protein excretion (in mg/[$m^2 \times$ h]) and the urinary protein/creatinine ratio (in mg/mmol) were calculated. The mean of the three determinations was used for analysis.

Data Analysis

None of the patients included in this report was enrolled in a preliminary communication published earlier by some of us.[9] The study protocol had been approved by the local Ethics Committees and by the participants. Female subjects of childbearing potential were excluded from the trial because of the possible fetal and neonatal toxicity. Pill count and pharmacy records were used to assess adherence to prescribed irbesartan. The length–weight equation developed by Haycock et al was used to estimate body surface area.[10] Results are given as median and interquartile range (which extends from the value at centile 25 to that at centile 75 and includes half of the data points), as relative frequency, or depicted as a "box and whiskers plot" (boxes are median and interquartile ranges, vertical lines are ranges). Nonparametric analysis of variance for repeated measurements, the McNemar change test (with the Yates correction for continuity), and simple regressions with the coefficient of correlation r_s^2 were used for analysis. A P value $<$ .05 was regarded as statistically significant.

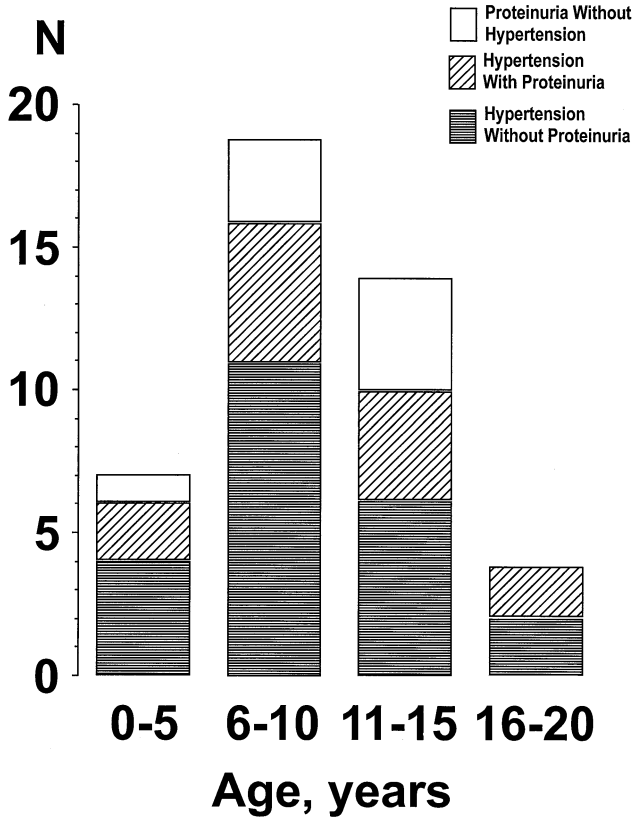

FIG. 1. Age distribution and disease conditions in 44 pediatric patients with chronic kidney diseases (27 male and 17 female subjects) included in the study.

Results

Characteristics of the Patients

The age distribution of the 44 patients and the corresponding disease conditions are shown in Fig. 1.

Tolerability and Side Effect Profile

A 12-year-old normotensive boy with pathologic proteinuria reported the appearance of elevated, erythematous pruritic wheals surrounded by an area of erythema involving the head and the trunk 2 h after a first dose of irbesartan. Swelling of the mouth, tongue, and eyelids was not reported. As a consequence, he withdrew from irbesartan. In the remaining patients, the frequency of abdominal pain, constipation, cough, diarrhea, dizziness, edema, fatigue, headache, insomnia, myalgia, orthostasis, and rash was similar before and during irbesartan treatment (Table 1). Hence, no further patient withdrew from irbesartan.

Plasma sodium slightly but significantly decreased, whereas plasma potassium significantly increased. Packed cell volume, plasma aminotransferases, creatine kinase, creatinine, and uric acid were not influenced by the use of irbesartan. In none of the patients did plasma potassium and sodium levels change by >0.5 mmol/L and 5 mmol/L. In none of the patients did circulating uric acid and creatinine levels change by >20% (Table 2).

Table 1. Adverse clinical experiences before and with irbesartan in 44 pediatric patients with chronic kidney diseases

	Hypertension Without Proteinuria		Hypertension and Proteinuria		Proteinuria Without Hypertension		All Patients	
	Before Irbesartan	With Irbesartan	Before Irbesartan	With Irbesartan	Before Irbesartan	With Irbesartan	Before Irbesartan	With Irbesartan
Patients, *N*	23	23	13	13	8	8	44	44
Abdominal pain, *N*	1	1	1	1	0	0	2	2
Constipation, *N*	1	3	0	0	1	1	2	4
Cough, *N*	1	0	2	2	0	0	3	2
Diarrhea, *N*	0	0	2	2	1	1	3	3
Dizziness, *N*	0	0	2	2	1	1	3	3
Edema, *N*	0	0	0	0	0	1*	0	1*
Fatigue, *N*	3	3	0	0	0	0	3	3
Headache, *N*	0	0	0	0	0	0	0	0
Insomnia, *N*	1	2	0	0	0	0	1	2
Myalgia, *N*	0	0	0	0	0	0	0	0
Nausea, *N*	0	0	0	0	0	0	0	0
Orthostasis, *N*	2	0	0	0	0	0	2	0
Rash, *N*	0	0	0	0	0	0	0	0
Patients with adverse events, *N*	5	6	3	2	3	3	11	11

* Elevated, erythematous pruritic wheals surrounded by an area of erythema involving the head and trunk 2 h after a first dose of irbesartan (see text). Patient withdrew from study.

Table 2. Laboratory safety values (median and interquartile range) before and with irbesartan in 43 pediatric patients with chronic kidney diseases

	Hypertension Without Proteinuria		Hypertension With Proteinuria	
Patients, *N*	23	23	13	13
Packed cell volume, L/L	0.39 (0.36–0.42)	0.39 (0.36–0.41)	0.40 (0.39–0.42)	0.39 (0.38–0.41)
Plasma aspartate aminotransferase, U/L	35 (24–36)	28 (20–36)	24 (22–36)	25 (24–36)
Plasma alanine aminotransferase, U/L	24 (13–31)	24 (14–32)	15 (12–30)	13 (12–24)
Plasma creatine kinase, U/L	85 (45–145)	84 (42–130)	55 (28–126)	55 (26–135)
Plasma sodium, mmol/L	139 (136–140)	137* (135–139)	138 (135–140)	136 (135–139)
Plasma potassium, mmol/L	4.2 (4.0–4.5)	4.4* (4.2–4.6)	3.9 (3.6–4.0)	4.1 (3.9–4.4)
Plasma creatinine, μmol/L	76 (65–85)	75 (65–83)	74 (56–94)	70 (65–80)
Plasama uric acid acid, μmol/L	388 (267–420)	378 (280–434)	331 (275–368)	347 (265–378)

Values noted in the patient who withdrew from the study are not given.
* $P < .03$ and †$P < .01$ *v* before irbesartan.

Hypertension

Before irbesartan, arterial pressure was 152 (142–166)/92 (85–96) mm Hg in the 36 patients with arterial hypertension. The initial irbesartan dose of 2.6 (2.2–2.9) mg/kg body weight once a day (71 [59–102] mg/m^2 body surface area once a day) was doubled in 26 of the 36 patients. At the end of the study, the dose of irbesartan was 4.1 (3.1–5.0) mg/kg (113 [98–168] mg/m^2 body surface area) once a day in the 36 hypertensive patients. The use of irbesartan for 18 weeks was associated with a decrease ($P < .005$) in arterial pressure by 17 (13–22)/10 [7–12] mm Hg up to 136 [128–148]/ 83 [79–87] mm Hg (Fig. 2). At that time, both systolic and diastolic blood pressure were below centile 95 in 20 of the 36 patients with arterial hypertension. Plasma albumin (38 [36–40] *v* 39 [36–41] g/L), heart rate (80 [74–83] *v* 76 [70–84]/min), body weight (33.1 [23.6–50.0] *v* 33.8 [23.8–49.9] kg), and body surface area (1.19 [0.93–1.40] *v* 1.20 [0.94–1.40] m^2) were similar before and with irbesartan. The effect of irbesartan on arterial pressure (20 [15–22]/9 [7–11] *v* 16 [11–22]/10 [7–13] mm Hg) and its dose (4.1 [3.1–4.9] *v* 4.0 [3.1–5.2] mg/kg body weight once a day) were not statistically different in 16 patients with normal renal function and in the remaining 20 patients. Furthermore, the effect on arterial pressure was similar in "pretreated" (18 [11–22] mm Hg; $N = 12$) and "nonpretreated" (16 [13–22] mm Hg; $N = 24$) patients. Linear regression analysis failed to disclose any relationship between patient age and final irbesartan dose, expressed either in mg/kg body weight daily or in mg/m^2 body surface area daily. Further regression analysis failed to demonstrate a significant relationship between irbesartan doses, expressed either in mg/kg body weight daily or in mg/m^2 body surface area daily, and change in arterial pressure. Finally, no significant correlation was noted between patient age and the influence of irbesartan on arterial pressure.

Proteinuria

Before irbesartan treatment, urinary protein excretion ranged from 51 to 204, median 126 mg/(m^2 × h) in the 20 patients with overt proteinuria who completed the study. The urinary protein excretion was similar in patients with (144 [89–150] mg/[m^2 × h]) and without (101 [74–129] mg/[m^2 × h]) arterial hypertension. In the 20 patients, overnight urinary protein significantly decreased during treatment with irbesartan by 52 (0–75) mg/(m^2 × h) ($P < .01$), whereas plasma albumin significantly ($P < .05$) increased by 4 [1–5] g/L: from 29 [21–30] to 33 [24–35] g/L, as depicted in Fig. 3. Urinary protein excretion decreased by ≥25%, namely, from 27% to 93% in 13 of the 20 patients with overt proteinuria.

A very close correlation was noted between the urinary protein excretion (in mg/[m^2 × h]), taken as an independent value, and the urinary protein/creatinine ratio (in mg/mmol), taken as a dependent value: $y = 5.02 \times$; $r_s^2 = 0.82$, $P < .0001$). In the seven patients with proteinuria but without hypertension who completed the study, the irbesartan dose was 2.9 (2.0–4.8) mg/kg body weight once a day (74 [62–127] mg/m^2 body surface area). In these patients, arterial pressure was similar before (114 [101–120]/63 [57–70]) and during (112 [98–118]/60 [55–70]) irbesartan treatment.

Interaction With Cyclosporine

In the eight patients treated with cyclosporine, the dose and the trough level of this agent were stable throughout the trial, as shown in Table 3.

Discussion

Adherence to the recommended regimen of care and persistence with it over time are common concerns in medical practice. Observations in adults indicate that in one half of

Table 2. (continued)

Proteinuria Without Hypertension		All Patients	
7	7	43	43
0.40 (0.39–0.41)	0.39 (0.37–0.42)	0.39 (0.36–0.42)	0.39 (0.35–0.41)
30 (25–36)	29 (24–30)	25 (24–36)	28 (20–36)
20 (14–32)	24 (15–31)	18 (12–31)	20 (12–31)
34 (27–82)	34 (27–80)	55 (33–145)	55 (31–130)
139 (138–140)	138 (137–139)	138 (136–140)	137† (135–139)
4.2 (4.0–4.6)	4.3 (4.1–4.6)	4.1 (3.9–4.5)	4.3† (4.1–4.6)
78 (67–87)	77 (73–81)	76 (61–85)	75 (65–83)
286 (258–347)	301 (250–359)	331 (269–420)	335 (265–434)

individuals with hypertension, arterial pressure is controlled, and one half of them stop taking their drugs during the initial year of treatment. Persistence varies with individual drugs, and adverse effects are the primary culprits. Adherence to the recommended antihypertensive regimen is also better in patients who are prescribed fewer drugs.[11] The present experience in pre–school-aged children, older children, and male adolescents with chronic kidney diseases given irbesartan for 18 weeks in a dose of approximately 4 mg/kg body weight (or 110 mg/m^2 body surface area) confirms the results of large trials in hypertensive adults treated with this drug, which blocks the binding of angiotensin II to type 1 angiotensin receptors. The major consistently observed advantages of irbesartan and other angiotensin antagonists are outstanding tolerability, low side effect profile, and use on a once-a-day basis.[1–5] Furthermore, the present limited experience confirms the ability of this drug to reduce overt proteinuria, a recognized surrogate marker of the efficacy of drugs in retarding the progression of kidney disease.[3–5]

This discussion will first focus on the antihypertensive and antiproteinuric effectiveness and the safety of irbesartan in this study. Despite the statistically significant and clinically relevant decrease in arterial pressure, irbesartan failed to normalize blood pressure in a large proportion (44%) of our hypertensive patients with chronic kidney diseases. This observation is probably related to the fact that arterial hypertension was moderate to severe in approximately 80% of the patients included in the survey. Hypertension and proteinuria are the most important factors that modulate progression in chronic kidney diseases.[12] Antihypertensive drugs mitigate progression, and this has been traditionally attributed to their blood pressure lowering action. It is agreed, however, that in chronic kidney diseases, angiotensin converting enzyme (ACE) inhibitors are superior to other drugs.[12] One limiting adverse effect in a minority of patients given ACE inhibitors is cough, an effect that does not occur with angiotensin antagonists.[13,14] Data in adult patients with kidney diseases have shown that angiotensin antagonists are as effective as ACE inhibitors in reducing pathologic proteinuria and slowing disease progression.[15] In the present study, treatment with irbesartan was associated with statistically significant but clinically irrelevant decreases in circulating sodium and increases in circulating potassium. However, no tendency toward higher circulating creatinine was observed. Hyponatremia, hyperkalemia, or renal failure have been previously reported in adults given angiotensin antagonists and in children and adults given ACE inhibitors. The effect on circulating sodium and potassium results from the suppression of the secretion of aldosterone driven by angiotensin II. In conditions in which glomerular filtration rate is critically dependent on angiotensin II (such as bilateral renal artery stenosis, heart failure, or volume depletion), blockade of the renin–angiotensin II–aldosterone system with either ACE inhibitors or angiotensin II antagonists can induce acute renal failure.[1]

The very attractive pharmacokinetic properties of irbesartan include an almost complete intestinal absorption of approximately 80% that is not affected by food, and a long elimination half-time of approximately 15 h that is not significantly altered by the presence of kidney disease. Furthermore, irbesartan does not require biotransformation for its pharmacologic activity.[1,2] Finally, our experience in patients concurrently treated with cyclosporine confirms data indicating that there are no interactions between irbesartan and other drugs.[16] In this pediatric study, the antihypertensive properties of irbesartan and its doses were age independent but were body weight and body surface area dependent.[1,2] These data provide support to a small, very recent study indicating that the pharmacokinetics of

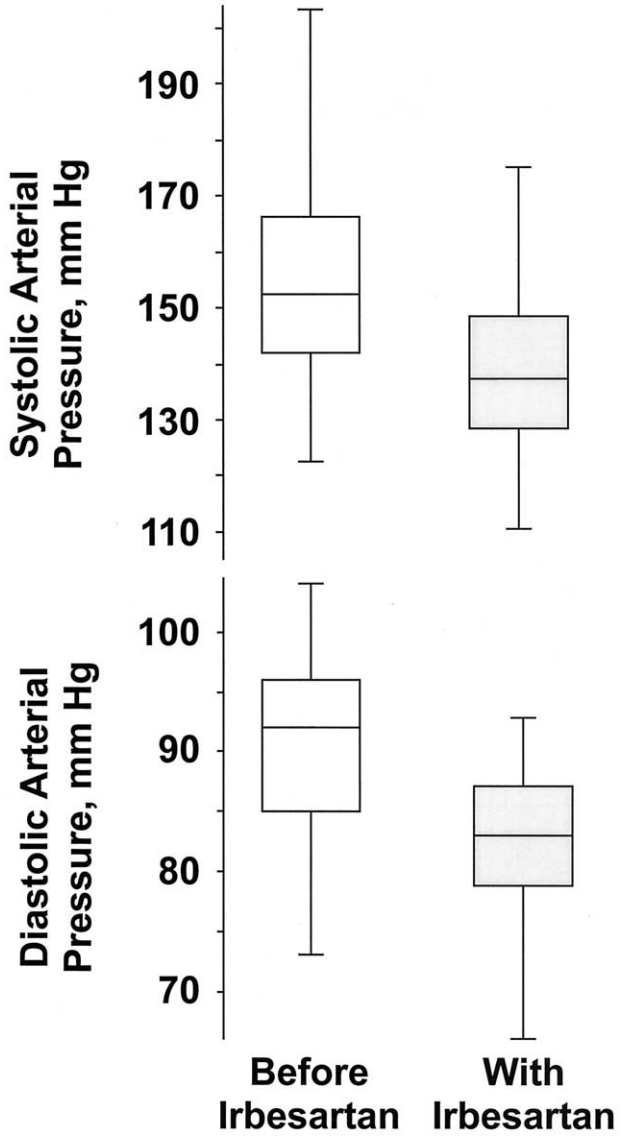

FIG. 2. Systolic and diastolic arterial pressure before and with irbesartan in 36 hypertensive patients with chronic kidney diseases. Both systolic and diastolic arterial pressure were significantly lower with irbesartan ($P < .005$). Results are given as "box and whiskers plot." In this plot, **boxes** are median and interquartile ranges, and **vertical lines** are ranges.

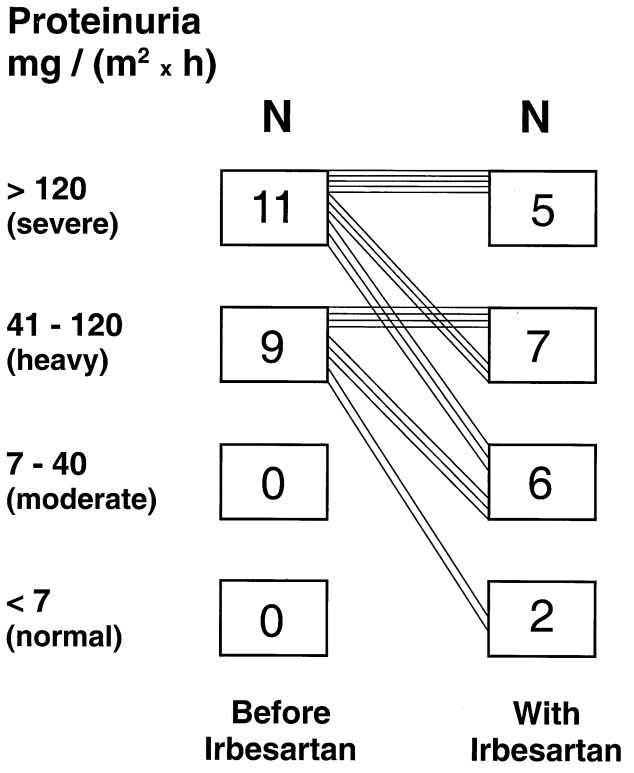

FIG. 3. Urinary protein excretion before and with irbesartan in 20 pediatric patients with overt proteinuria.

irbesartan is similar between children aged 6 to 18 years and adults.[17]

Like ACE inhibitors, angiotensin antagonists reduce the activity of the renin–angiotensin II–aldosterone system. Nonetheless, there are two differences: the receptors that are affected, and the effect on kinins.[18,19] Angiotensin II activates both type 1 and type 2 receptors. As a result, inhibition of angiotensin II formation with an ACE inhibitor will diminish the activity of both receptor types. In contrast, angiotensin antagonists diminish only type 1 activity. The type 1 receptor mediates the vasoconstrictor effect of angiotensin II and is generally thought to mediate angiotensin II–induced growth in the ventricle and the arterial wall. Several recent studies suggest that the type 2 receptor exerts the opposite effects from the type 1 receptor. For example, activation of the type 2 receptor exerts antigrowth, antihyperthrophic, proapoptotic, and hypotensive effects. Angiotensin converting enzyme is also a kininase. As a result, inhibiting this enzyme with an ACE inhibitor increases kinin levels, an effect not observed with angiotensin antagonists. It is presumed that the absence of kinin accumulation accounts for the lack of cough with angiotensin antagonists. However, kinin accumulation may also mediate some of the beneficial effects of ACE inhibition. At this time, it remains unclear whether angiotensin antagonists are a minor addition (an ACE inhibitor without cough) or a major advance. Outcome data are needed before angiotensin II receptor blockers are generally recommended instead of ACE inhibitors.[1]

Limitations of the present study include its uncontrolled design and the lack of a comparison agent. More importantly, the impact of angiotensin antagonists on progression of chronic kidney disease and on target organ damage in childhood cannot be established from our data. It is worthy of mention, however, that this statement also holds true for the remaining classes of antihypertensive drugs that are widely used in childhood.[6] Large trials performed in adult patients demonstrate the benefits of diuretics, β-blockers, ACE inhibitors, and angiotensin II receptor blockers on target organ damage.[20] On the contrary, the results of large trials demonstrate that postsynaptic α_1-receptor blockers, direct vasodilators, and perhaps even

Table 3. Dosage and trough blood levels of cyclosporine in 8 pediatric patients (5 boys and 3 girls, aged 4.8 to 18 years, median 9.4 years) with chronic kidney diseases before and with irbesartan

	Before Irbesartan	With Irbesartan	*P* Value
Cyclosporine dosage, mg/kg daily*	4.5 (4.0–5.1)	4.4 (4.0–5.0)	NS
Cyclosporinemia, μg/l	121 (85–159)	130 (101–152)	NS

NS = not significant.
Results are given as median and interquartile range.
* Given in two daily doses.

some dihydropyridine calcium channel blockers do not positively influence the long term outcome.[9,21]

In conclusion, we believe that, despite these limitations, the present data indicate that irbesartan is an effective and very well tolerated agent for the management of chronic kidney diseases in children.

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