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BRIEF REPORT

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Candesartan cilexetil in children with hypertension or proteinuria: preliminary data

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Abstract The angiotensin II receptor blockers irbesartan and losartan effectively reduce blood pressure and proteinuria in childhood. We were impressed by the neutral taste and the small size of the candesartan cilexetil tablets. This angiotensin II receptor blocker was used during 4 months in 17 pediatric patients (aged 0.5–16, median 4.5 years) with chronic arterial hypertension (n=6), overt proteinuria (n=2), or both (n=9). The initial candesartan dose of 0.23 (0.16–0.28) mg/kg body weight once daily (median and interquartile ranged) was doubled in ten patients [final dose 0.35 (0.22–0.47) mg/kg body weight]. No adverse clinical experiences were noted on candesartan. Candesartan increased plasma potassium by 0.3 (0.0–0.8) mmol/l (P<0.01). In children with arterial hypertension, blood pressure decreased by 9 (3–13)/9 (3–18) mmHg (P<0.01); in those with overt proteinuria the urinary albumin/creatinine ratio decreased by 279 (33–652) mg/mmol (P<0.05). In conclusion, in children candesartan reduces blood pressure and proteinuria with an excellent short-term tolerability profile.

Keywords Candesartan · Child · Hypertension · Proteinuria

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Introduction

The angiotensin II receptor blockers irbesartan (150–300 mg once daily), losartan (50–100 mg once daily), and candesartan cilexetil (16–32 mg once daily) are widely prescribed to treat adult patients with arterial hypertension or proteinuria [1–3]. Recent observations demonstrate that irbesartan [4–6] and losartan [7–9] effectively reduce blood pressure and pathological proteinuria also in children. In adult patients with arterial hypertension or pathological proteinuria, candesartan is as effective as irbesartan or losartan [1–3]. We were positively impressed by the neutral taste and the small size of the candesartan cilexetil tablets, which can be easily crushed and dissolved in a small amount of water. Considering that in childhood factors such as the ease of administration and the palatability come into play to determine which agent is optimal when there are several agents of similar efficacy [10, 11], we prescribed candesartan cilexetil in some of our patients, especially in those refusing the tablets of irbesartan or losartan.

Patients and methods

The purpose of this report is to describe our preliminary, not commercially sponsored experience with candesartan during 4 months in 17 pediatric patients (7 girls and 10 boys, aged 0.5–16, median 4.5 years) with chronic arterial hypertension (systolic or diastolic arterial pressure persistently above the 95th percentile for age, weight, and gender, n=6), overt proteinuria (urinary albumin/creatinine ratio >20 mg/mmol on early morning urine, n=2), or both (n=9) [12]. The underlying conditions were glomerular disease (n=11), polycystic kidney disease (n=3), renal transplant (n=2), and essential hypertension (n=1). Renal function was either normal (normal plasma creatinine for age and gender, n=9), moderately reduced (plasma creatinine increased but less than 200 μmol/l, n=5), or strongly reduced (plasma creatinine ranging between 200 and 450 μmol/l, n=3). Of the 17 patients, 9 were on medication

with a variety of antihypertensive drugs: hydrochlorothiazide (n=3), furosemide (n=3), propranolol (n=1), amlodipine (n=2), or nifedipine (n=1). The regularly scheduled antihypertensive regimen had not been changed for at least 6 weeks and was continued during treatment with candesartan. Before initiating candesartan and at each follow-up visit, sitting (>10 min) blood pressure and heart rate were measured, blood collected for determination of packed cell volume, creatinine, urea, uric acid, sodium, potassium and albumin, and an early morning urine collected for determination of albumin and creatinine, according to our standard procedure [5]. Candesartan cilexetil was started at a once-a-day morning dose of 2 (body weight <10 kg), 4 (body weight between 10 and 19 kg), or 8 mg (body weight 20 kg or more). The dosage of candesartan was doubled if necessary: (a) failure to decrease systolic blood pressure by at least 10 mmHg or (b) systolic or diastolic blood pressure above the 90th centile after 4–8 weeks. Patients were monitored for the occurrence of adverse clinical experiences by means of a previously reported questionnaire [5]. The results are given as median and interquartile range (which extends from the value at the 25th centile to that at the 75th centile and includes half of the data points). Comparison of values before and with treatment with candesartan was made using the nonparametric Wilcoxon matched pairs signed rank sum test. Statistical significance was set at P<0.05.

Results

In the 17 patients the initial candesartan cilexetil dose averaged 0.23 (0.16–0.28) mg/kg body weight. The dosage was doubled in ten patients with arterial hypertension. The final dose averaged 0.35 (0.22–0.47) mg/kg body weight. Abdominal pain, constipation, cough, diarrhea, dizziness, edema, fatigue, headache, insomnia, myalgia, orthostasis, and rash never developed during medication with candesartan. Hence, no patient withdrew from treatment with this agent. Heart rate [94 (80–119) versus 90 (76–114)/min], body weight [19.6 (11.9–35.1) versus 18.6 (12.0–34.0) kg], packed cell volume [0.36 (0.32–0.39) versus 0.36 (0.34–0.40)], circulating creatinine [65 (53–75) versus 70 (51–79) μmol/l], sodium [138 (136–139) versus 136 (134–139) mmol/l], uric acid [230 (209–257) versus 238 (215–248) μmol/l], and albumin [37 (26–40) versus 34 (29–42) g/l] were not significantly influenced by the use of candesartan. The use of candesartan significantly (P<0.01) increased plasma potassium by 0.3 (0.0–0.8) mmol/l: from 4.2 (3.9–4.5) to 4.9 (4.2–5.0) mmol/l. The effect on potassium was similar in patients with and without arterial hypertension.

In the subgroup of 15 children with arterial hypertension, blood pressure significantly (P<0.01) decreased by 9 (3–13)/9 (3–18) mmHg: from 122 (116–125)/81 (72–89) to 114 (108–121)/72 (66–77) mmHg. The effect on blood pressure was similar in subjects with and without overt proteinuria. In the subgroup of 11 patients with overt proteinuria candesartan significantly decreased (P<0.05) the urinary albumin/creatinine ratio by 279 (33–652) mg/mmol: from 453 (221–1,259) to 315 (94–367) mg/mmol. In these subjects plasma albumin levels were similar without [28 (26–30) g/l] and with candesartan [30 (28–33) g/l].

Discussion

Antihypertensive drugs are not investigated in children before approval for marketing in adulthood and information is mostly acquired during clinical use. This preliminary, uncontrolled experience in children given the angiotensin II receptor blocker candesartan cilexetil during 4 months at a dose of approximately 0.35 mg/kg body weight once daily confirms the results of large trials with adult patients indicating that candesartan effectively reduces blood pressure and pathological proteinuria with an excellent short-term tolerability profile [1, 2].

The present data confirm that angiotensin II receptor blockers, like converting enzyme inhibitors, increase potassium level. Although these agents generally raise potassium by less than 0.5 mmol/l, more prominent hyperkalemia sometimes occurs in kidney diseases. Physicians sometimes respond to increases in potassium level by discontinuing these drugs. While close monitoring is required, several steps minimize the likelihood of developing hyperkalemia, including discontinuing drugs that impair potassium excretion and counseling against the use of salt substitutes that contain potassium. Finally thiazide diuretics or, with rather advanced kidney disease, loop diuretics are particularly effective in minimizing hyperkalemia [13].

We never prescribed candesartan in newborn infants, because at this age renal function strongly depends on the renin-angiotensin II system, and in female subjects of childbearing potential, because angiotensin II receptor blockers are fetotoxic [14, 15].

The antihypertensive or antiproteinuric efficacy and the safety profile of candesartan (0.35 mg/kg body weight) noted in the present pediatric uncontrolled experience is similar to that of irbesartan 4.0 mg/kg body weight [4–6] and losartan 0.8–1.4 mg/kg body weight [7–9] both in controlled as well as in uncontrolled trials. Hence, these data support the assumption that currently available angiotensin II receptor blockers are equivalent with respect to arterial hypertension and pathological proteinuria [1, 2]. Questions have been raised about the appropriateness of the equivalence among all angiotensin II receptor blockers [3]. Nonetheless, assuming a similar effectiveness, the taste and the ease of administration greatly affect drug selection and prescribing practice of pediatricians [10, 11]. Consequently, the neutral taste and the small size of the candesartan cilexetil tablets indicate that this angiotensin II receptor blocker might be a very attractive agent for the treatment of arterial hypertension and pathological proteinuria in childhood. The assumption deserves confirmation by studies specifically addressing the taste preferences of children [10]. Interestingly, palatability has never been

studied in children with respect to medical treatment of arterial hypertension.

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