Hypertensive rebound after angiotensin converting enzyme inhibitor withdrawal in diabetic patients with chronic renal failure

Sir,
Although angiotensin-converting enzyme (ACE) inhibitors are considered a milestone in the treatment of hypertension and microalbuminuria in diabetic patients [1,2], some cautionary notes were reported in the setting of significant reduction of renal function [3–5]. Discrepancy between long-term trials [1,2] and anecdotal reports [3–5] is probably due to the different selection of patients in trials and in clinical practice. Little is mentioned, however, about withdrawal of ACE-inhibitors in late phases of renal failure.

We describe two patients with type 1 diabetes and moderate–several renal failure who developed a rebound hypertension following discontinuation of very low doses of ACE-inhibitors, despite the concomitant increase of other antihypertensive drugs at clinically corresponding doses.

Cases. Patient 1 is a 40-year-old woman, with type 1 diabetes since 1971 (BMI 20.7 kg/m²), hypertension since 1989, laser-treated diabetic retinopathy, proteinuria (>30 mg/dl) diagnosed in 1988, clinical diagnosis of diabetic nephropathy. At start of regular nephrologic follow-up (1996), renal ultrasound scan displayed normal renal morphology and volume, and hyperchogenicity. At that time, she was treated with furosemide 50 mg/day, verapamil 240 mg/day and enalapril 20 mg/day. A renal dynamic nuclear scan, performed during ACE-inhibitors revealed dyshomogeneous and reduced
parenchymal uptake, with contracted and slowed symmetric curves (ACE-inhibitors had been taken for 9 years). Glycated haemoglobin ranged from 7.8–9.5%, serum creatinine from 2.5–3 mg/dl (creatinine clearance from 32–20 ml/min), proteinuria from 0.8–1.8 g/day. In consideration of the severe functional impairment without nephrotic proteinuria, enalapril dose was tapered over a 2-month period to 5 mg/day and doxazosin 2 mg/day was added.

The patient carefully performed home blood pressure self-monitoring (blood pressure 135/80 mmHg). A second renal nuclear scan showed a significant improvement of renal flow. Enalapril was discontinued and doxazosin raised to 4 mg/day. Three days after withdrawal, the patient found home blood pressure levels of 140–150/95–105 mmHg. After 2 days, during which she had strong headaches, she self-administered enalapril 2.5 mg/day, with complete normalization of blood pressure within 2 days (130/75 mmHg). Doxazosin dose was reduced to 2 mg/day. When the patient reported the increase in blood pressure (which occurred during a holiday period), the medical staff was sceptical on a cause-effect relationship; therefore, after 3 months, we decided, together with the patient, the temporary discontinuation of enalapril. Despite the concomitant increase of the dose of doxazosin to 4 mg/day, the withdrawal of enalapril (2.5 mg/day) induced hypertension (145/100 mmHg) with similar time profile (2–3 days). An echodoppler was negative for the presence of arterial renal stenosis. Enalapril 2.5 mg/day was reintroduced. The patient received a successful kidney–pancreas graft in June 1998.

A similar hypertensive rebound was observed in patient 2: a 59-year-old male with type 1 diabetes since 1967, hypertension since 1988, laser treated retinopathy and proteinuria since 1980. Renal functional impairment was present since 1992 (serum creatinine 1.4 mg/dl). In 1995, a renal biopsy displayed diffuse nodular diabetic glomerulosclerosis, in advanced sclerotic evolution, with widespread vascular damage. The patient was treated with ACE-inhibitors continuously for 3 years.

In 1997, renal ultrasound scan showed kidneys of normal shape and volume, and increased echogenicity. Renal dynamic nuclear scan, performed during fosinopril therapy (5 mg/day), showed dyshomogeneous and reduced parenchymal uptake with contracted and slowed symmetric curves.

In February 1997 serum creatinine was 2.2 mg/dl, creatinine clearance 55 ml/min, proteinuria 1.9 g/24 h. Anti-hypertensive treatment consisted of fosinopril 5 mg/day, furosemide 100 mg/day, transdermal clonidine 1 mg/week and doxazosin 2 mg/day. At home, blood pressure ranged from 150/90–135/80 mmHg; the patient performed blood pressure self-monitoring. Fosinopril was discontinued for hyperkalaemia and doxazosin increased to 4 mg/day. Ten days after the therapeutic changes, the patient went to the emergency room with a symptomatic hypertensive crisis at 220/130 mmHg. This was the first hypertensive crisis ever reported by the patient. After regression of the crisis, fosinopril was restarted (10 mg/day), and doxazosin increased to 8 mg/day. The patient performed a strict home self-monitoring of blood pressure, which decreased to the usual levels within 3 weeks. Also in this case renal echodoppler was negative for the presence of renal artery stenosis. Since this episode, fosinopril was taken without discontinuation. In February 2000, serum creatinine was 3.5 mg/dl, creatinine clearance 20 ml/min, proteinuria 0.9 g/day.

Comment. This anecdotal report regards two patients with type 1 diabetes and diabetic nephropathy, with moderate to severe renal functional impairment, treated for several years with ACE-inhibitors. They developed a sharp increase in blood pressure, with a hypertensive crisis in one case, at discontinuation of ACE-inhibitors, regularly taken at very low doses, considered sub-therapeutic for hypertension control. It is remarkable that this ‘discontinuation syndrome’ took place despite the concomitant increase in doses of other antihypertensive drugs and in the absence of other causal factors, such as poor compliance, reduced absorption of oral drugs due to gastroenteritis or vomiting, and self-administration of non-steroid anti-inflammatory drugs.

A symptomatic rebound of hypertension after withdrawal of ACE-inhibitors at low doses has, to our knowledge, never been reported. Our observation suggests that ACE-inhibitors, which are widely used and considered as a first line tool for preventing progression of renal diseases [1,2], should be handled with careful and strict surveillance not only at the start but also at withdrawal of treatment, at least in long-term treated diabetic patients with renal failure.

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