OACE inhibition does not interfere with acute extrarenal or renal potassium disposal in chronic renal failure

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Abstract. The influence of angiotensin converting enzyme (ACE) inhibition on acute extrarenal and renal potassium elimination in stable chronic renal failure has been examined in 10 male patients median age 44 y; mean Clcr 42 ml·min⁻¹·1.73 m⁻². In a double blind, placebo-controlled cross-over study, K⁺ 0.3 or 0.4 mmol·kg⁻¹ body weight was infused IV on two occasions while the patients also received an infusion either of placebo or 0.5 mg of the ACE inhibitor perindoprilat in random order. Plasma K⁺ levels and urinary K⁺ excretion were measured at regular intervals. During the study patients adhered to an isocaloric diet providing a standardized daily intake of potassium and sodium (50 mmol K⁺ and 40 mmol Na⁺).

The median rise in plasma K⁺ was not significantly different after placebo (ΔK 0.66 mmol·l⁻¹) compared with to the infusion of perindoprilat (ΔK 0.66 mmol·l⁻¹). The median baseline urinary K⁺ excretion rate was 6.5 mmol·3 h⁻¹ before the placebo infusion and 5.9 mmol·3 h⁻¹ before infusion of perindoprilat. During the potassium load, the urinary excretion rate rose to 16.1 mmol·3 h⁻¹ (after placebo) and 15.1 mmol·3 h⁻¹ after perindoprilat in the first 3 h, and it returned almost to the baseline value within the next 3 h (5.6 mmol·3 h⁻¹ after placebo and 5.7 mmol·3 h⁻¹ after perindoprilat); the differences were not statistically significant.

With perindoprilat a decrease in mean arterial blood pressure and ACE activity, an increase in renin plasma activity and a decrease in aldosterone concentrations were observed compared to the placebo infusion. There was no significant differences plasma in adrenaline or insulin levels after either infusion.

Thus, ACE inhibition did not interfere either with the extrarenal or the renal disposal of an acute potassium load in patients with chronic renal failure.

Key words: ACE Inhibition, Renal failure, Perindoprilat; potassium, extrarenal disposal, renal excretion, hyperkalaemia

The kidney is able to excrete no more than 50% of an acute potassium load in the first 4 h [1-3]. Additional extrarenal mechanisms are responsible for buffering an acute potassium load and for the prevention of hyperkalaemia, including a transmembranous intracellular shift of potassium ions mediated by insulin, adrenaline and aldosterone, and transcellular exchange of potassium ions for protons [4-6]. In the long-term control of the plasma potassium concentration, however, the kidney plays the major role [6]. The renal functions involved in potassium homeostasis are glomerular filtration, and the reabsorption and secretion of potassium in the far distal tubule under the influence of aldosterone. It is well recognised that patients with chronic renal failure have impaired ability to handle acute exogenous potassium loads [3, 6-9], but hyperkalaemia is usually not found before the terminal stage of chronic renal failure, except in certain risk groups, namely the elderly and diabetics, in whom hyporeninaemic hypoaldosteronism (Schambelan syndrome) is common [10].

After administration of angiotensin-converting-enzyme (ACE) inhibitors, a slight increase in plasma K⁺ is noted in patients treated for hypertension or congestive heart failure when they have normal renal function [11]. The rise in plasma K⁺ concentration after ACE inhibition is more pronounced in patients with impaired renal function, and some patients develop severe life threatening hyperkalaemia [12-15]. It is thought that the increase in plasma K⁺ primarily results from chronic reduction in the angiotensin II-mediated secretion of aldosterone by ACE inhibitors. The increase in plasma potassium levels after long-term ACE inhibitor treatment is inversely related to the glomerular filtration rate (GFR) [11, 15]. This observation suggests that impaired renal mechanisms of potassium excretion are also important [6].

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A recent study in healthy volunteers with normal renal function showed that the maximal increase in plasma K⁺ levels during an acute intravenous KCl load was similar after administration of placebo and the ACE inhibitor enalapril [16]. This did not address the issue, however, of whether acute potassium homeostasis after a potassium load in patients with renal failure would be affected by ACE inhibitors. This point is of relevance to the safety of ACE inhibitor therapy, but it appears not to have been investigated. To examine whether ACE inhibition interfered with renal and/or extrarenal handling of an acute potassium load in these circumstances, we have conducted a prospective, double blind, cross-over study in 10 patients with stable chronic renal failure. The patients received an acute intravenous KCl load while receiving, in random order, an infusion either of placebo or the ACE inhibitor perindoprilat.

Patients and methods

Patients

Ten male patients (median age 44 [29-69] y) with stable chronic renal failure (mean endogenous creatinine clearance 42 [25–72] ml min⁻¹·1.73 m⁻²) were enrolled in the study. In two patients IgA glomerulonephritis (GN) and in one mesangio proliferative GN had been diagnosed by renal biopsy; in two patients GN had been diagnosed on clinical grounds, but had not been confirmed by renal biopsy; one patient had autosomal dominant polycystic kidney disease, two patients had a history of malignant hypertension, one had reflux nephropathy and one had radiation nephritis. To avoid potential interference with potassium homeostasis, all medication was stopped 14 days before the start of the investigation with exception of calcium channel blockers to control blood pressure. All the patients had plasma K⁺ < 5 mmol l⁻¹ on repeated outpatient visits. All of them were clinically stable and none had significant heart disease or any evidence of malnutrition.

Protocol

The protocol of the present study was approved by the Ethics Committee of the University of Heidelberg. All the participants had given written, informed consent. The patients were examined using a double blind, cross-over placebo-controlled study design. They were equilibrated for 14 days on a diet providing a standardised daily potassium and sodium load (50 mmol K⁺ and 40 mmol Na⁺). The diet was supplied as precooked, deep frozen meals. Dietary compliance was controlled by regular measurements of 24 h urinary K⁺ and Na⁺ excretion. On the morning of the 7th and 14th days, patients were admitted to the metabolic ward after a 12 h overnight fast. The investigation was performed with each subject supine in a quiet room. After blood samples had been taken, the patients received infusion of 10% KCl, diluted in 0.9% NaCl 450 ml for 90 min (Fig 1). The quantity of KCl in fusion was 0.4 mmol kg⁻¹ body weight, and it was reduced to 0.3 mmol kg⁻¹ if the baseline plasma potassium level was above 4.5 mmol l⁻¹. In parallel with the KCl infusion, either placebo or 0.5 mg of the ACE inhibitor perindoprilat was infused for 60 min (Fig 1). Using random numbers patients were allocated to receive the placebo or perindoprilat first.

Before the infusions were started, the patients emptied the bladder and blood samples were taken for determination of baseline plasma K⁺, Cl⁻, glucose and HCO₃ levels, angiotensin-converting enzyme (ACE) and plasma renin activity (PRA), aldosterone, insulin and adrenaline concentrations. The plasma K⁺ concentration was measured at 15, 30, 45, 60, 75, 90, 120 and 180 min. Hormonal and other blood measurements were repeated after 90 and 180 min, and ACE activity was determined after 60 and 180 min. Blood samples were collected without use of a tourniquet and were immediately centrifuged at 4°C (3000 rpm). Plasma was frozen at −20°C. Specimens for the determination of adrenaline and noradrenaline were frozen in liquid nitrogen and stored at −80°C. Urine was collected for 3 h from the start of the infusions and thereafter for further 3 h. Urine K⁺, Na⁺, Cl⁻, creatinine concentrations and osmolality were determined. Mean arterial blood pressure (MAP) and heart rate were measured throughout at regular intervals and a 12-lead ECG was recorded at 0, 60 and 90 min to monitor signs of hyperkalaemia.

Measurements

Na⁺ and K⁺ concentrations in plasma and urine were measured by flame photometry. The coefficient of variation of 10 replicate measurements of potassium in 5 plasma samples was 1.1 (0.5) %. Creatinine and glucose concentrations were determined with an autoanalyser, plasma chloride levels were measured with a chloridometer, and plasma carbon dioxide content (HCO₃) with an automatic blood gas analyser. PRA was measured by RIA, insulin by an enzymatic method, adrenaline by HPLC, and ACE by a kinetic method. MAP and heart rate were monitored oscillometrically with an automatic device (Dinamap).

Statistical analyses

The primary endpoints of the study were the increases in plasma potassium concentration and urinary potassium excretion rate during the potassium load. The values during infusion of perindoprilat were compared with those during infusion of placebo using Wilcoxon's test for paired observations. When more than two time points were involved, the Friedman test for repeated measurements and the Wilcoxon–Wilcox test were employed. A P value of 0.05 was considered significant. Data are given as median and range.