Lisinopril has no natriuretic effect in elderly: A study of the single-dose response in aged vs young individuals

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Abstract

In order to evaluate the short-term effect of angiotensin-converting-enzyme (ACE) inhibition on the renal water and electrolyte handling in healthy elderly, we compared the actions of a single oral dose of lisinopril (Prinivil, 20 mg) in 13 healthy individuals over 75 years of age (82.6 ± 5.8 yrs) with that of 6 healthy young subjects (26.2 ± 0.7 yrs). No variations in serum sodium were observed in either groups. In the young group, we observed an increase in sodium excretion and glomerular filtration rates (creatinine clearance). In the aged group, we did not find any increase in sodium excretion and GFR remained unchanged, while diuresis decreased. The possible mechanisms for this discrepancy are discussed. The aged kidney submitted to ACE inhibition reacts in a different way than the younger kidney and this could lead, at least theoretically, to sodium retention. The therapeutic use of ACE inhibitors should be carefully monitored when a natriuretic effect is required.

In the elderly, serum sodium levels are difficult to keep within normal range. The relationship between sodium and water is compromised by a progressive reduction of their intake and renal loss [1–7]. The growing use of drugs which act on sodium and water metabolism has led to such complications as hyponatremia and/or edema in this population of patients, in whom water, electrolyte and acid-base equilibrium are already difficult to maintain [8–13].

Angiotensin-converting-enzyme (ACE) inhibitors such as enalapril are largely prescribed for treatment of hypertension and congestive cardiac failure [14–16]. While renal complications associated with the use of these drugs are seen, alterations in serum sodium are rare. However the pathophysiological effects of ACE inhibitors are not yet entirely known and their use could lead to deleterious effects. A natriuresis and an increase in glomerular filtration rate (GFR) are well documented after ACE inhibitor use [17, 18]. However most studies have been on young individuals and there is a lack of information concerning older subjects.

Renal adaptation to changes in water and/or sodium metabolism is slower in elderly patients compared to younger individuals [1, 5, 19]. Thus, the question is whether a drug could become harmful over a short-term by altering this fragile balance.

We therefore decided to investigate the acute renal response to an oral single dose of lisinopril under usual diet and activity conditions in healthy subjects over 75 years of age and to compare them to younger individuals.
Patients and methods

This study was approved by the local hospital ethical committee (C.H.U. de Nancy) and informed consent was obtained from each individual.

Study population

Thirteen “very old” subjects (82.6 ± 5.8 yrs, 5 males and 8 females), were waiting for a placement in a nursing home. They were studied when hospitalized for a check-up. Criteria for inclusion included arterial pressure ≤150/95 mmHg, standard hospital diet (sodium = 6 g/d), and no abnormalities in blood chemistry. We excluded patients who had a stroke, cardio-vascular disease, diabetes mellitus, hypothyroidism or obstructive nephropathy, and those receiving diuretics, ACE inhibitors, vasodilators, non-steroidal anti-inflammatory drugs, digitalis, calcium channel blockers, steroids or potassium supplements.

Six consenting healthy medical students (5 males and 1 female, 26.2 ± 0.7 yrs) who had none of the aforementioned exclusion criteria were used as controls. They had no known diseases and were not taking any medication at the time of the study.

Study protocol

All subjects had their usual diet for at least three days preceding the study. During the study, meals were given as usual. Water intake was not limited. After 24 hrs of urine collection and blood sampling for baseline (T0), lisinopril (Prinivil, 20 mg) was given orally at 9 a.m. Urine was collected over three consecutive periods (T3, T6, T24): 3, 6 and 24 hrs after drug administration. After T3, T6, T24 urinary collections, the samples were mixed, in order to obtain data on cumulative excretion. A blood sample was taken at the end of each timed urinary collection.

Sodium, potassium, chloride, osmolality, creatinine, urea and uric acid levels in every collected sample of plasma and urine were assessed by routine hospital biochemical techniques.

Creatinine, osmolar and electrolyte clearances and fractional excretions (FEC) were obtained using standard formulas. Creatinine clearance was corrected to 1.73 m² BSA. Free-water clearance was calculated as urinary flow (diuresis) minus osmolar clearance. By analogy, effective water clearance (EWC) was diuresis minus clearance of electrolytes = V - CEL (CEL: clearance of electrolytes): \[V(U_{Na} + U_K)/(P_{Na} + P_K) \]

Statistical analysis

Paired t-test was used to compare paired data from the same group of persons. Non-paired Student’s t-test was carried out to compare the mean of the two groups.

Results

All baseline values for measured plasma and urinary parameters were within normal ranges in both groups [20–22]. A lower creatinine clearance was observed in the elderly subjects (p < 0.001) [23]. These results (see Table 1, T0) give evidence of normal fluid and electrolyte intakes at base line. However, changes in electrolyte excretions indicate different diets in normal living conditions between the elderly and younger subjects (Table 1).

Differences in responses appeared between the aged and young subjects (Figure 1).

a) Elderly: diuresis, sodium excretion and fractional sodium excretion decreased slightly during T3 and T6 periods. Potassium excretion and creatinine clearance did not vary significantly and effective water clearance remained positive.

b) Young: Creatinine clearance and sodium excretion increased significantly for T3 and T6 and diuresis for T6. Potassium excretion was not modified. Effective water clearance decreased dramatically.

No lisinopril-induced changes in arterial pressure were observed in either group.

Discussion

This study was conducted on two groups of healthy individuals with rigorous criteria of selection: age, absence of underlying or previous disease, no interfering drug treatment and careful preparation and execution of the preplanned protocol. Baseline values for blood chemistries, creatinine clearance, fractional excretion of sodium and chloride. [FECNa > 1.1% and FECCl > 0.7% (data not shown)] were in ranges considered as being normal for very old subjects [22, 24–30].

No drug-induced adverse effects were observed and plasma creatinine did not significantly increase during this acute oral test.