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Angiotensin-converting enzyme inhibition as a therapeutic principle in Bartter's syndrome

P. Jest[1], K. E. Pedersen[1], N. A. Klitgaard[1], N. Thomsen[3], K. Kjaer[2], and E. Simonsen[3]

Departments of [1] Clinical Chemistry and [2] Endocrinology, Odense University Hospital, and [3] Department of Medicine, Haderslev Hospital, Denmark

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Summary. The effect of captopril has been investigated in four patients with Bartter's syndrome treated for 12 weeks.

Baseline biochemistry showed normal serum aldosterone (mean 347 pmol·l^{-1}) and a mean serum renin of 217 mU·l^{-1}, and a considerable increase in serum renin during captopril treatment. Serum aldosterone decreased gradually during the study period to about half its initial value. The patients presented with a mean serum potassium of 2.5 mmol·l^{-1}, which rose to 3.4 mmol·l^{-1} on captopril. Lymphocytes showed a substantial captopril-induced increase in intracellular sodium (from 15 to 22.5 mmol·l^{-1} on average), but no change in the potassium content.

Captopril was well-tolerated. It may be an alternative to potassium-sparing diuretics for maintaining normal serum potassium levels in patients with Bartter's syndrome.

Key words: Bartter's syndrome, Hypokalaemia, Captopril; ACE-inhibitor, lymphocyte sodium and potassium, adverse effect, plasma renin, aldosterone

Patients with Bartter's syndrome present clinically with chronic abnormal potassium homeostasis characterized by massive renal loss of this cation and secondary severe hypokalaemia [1]. Many patients with Bartter's syndrome complain of fatigue and adynamia, although some are asymptomatic despite pronounced potassium depletion. Hyperreninism, hyperaldosteronism, hyperprostaglandinuria, juxtaglomerular hyperplasia and decreased angiotensin sensitivity are invariably present as in subjects with genuine Bartter's syndrome. However, the complex interplay between renal function, the renin-aldosterone system and cellular cation regulation is not fully understood [2, 3].

Most investigators in this field consider that activation of the renin-aldosterone axis is of secondary importance [4]. However, treatment with an aldosterone antagonist causes a modest increase in the plasma potassium level [5], which clearly indicates that hyperaldosteronism may aggravate renal potassium loss.

The emergence of angiotensin converting enzyme inhibitors has provided a tool for biochemical blockade of inappropiate aldosterone production. The present study has been performed to investigate the effects of captopril in patients with Bartter's syndrome.

Subjects and methods

Patients

Initially all patients were hospitalized for evaluation of their disease. Other causes of hypokalaemia, such as primary hyperaldosteronism, ectopic corticotropin producing tumours, renal tubular acidosis, familiar periodic paralysis, abuse of diuretics or laxatives and anorexia nervosa were excluded. Four patients, 2 women and 2 men, mean age 29 y (range 23–35 y), all fulfilling the clinical and biochemical criteria for Bartter's syndrome, participated in the study. The patients presented with spontaneous chronic hypokalaemia, hyperreninaemia, high aldosterone levels and normal blood pressure. Two of the patients had a family history of the disease. All had normal renal function. Initially all patients were treated with potassium chloride supplements, which did not lead to normalisation of the plasma potassium level. Three of the patients were partly sensitive to prostaglandin synthetase inhibitors. At the time of the investigation none of the subjects was taking any medicine except for that prescribed by the protocol.

Protocol

At least 2 weeks before the trial all medicines were withdrawn. In two patients (Nos 3 and 4), potassium supplementation had to be continued due to severe hypokalaemia. This treatment was discontinued after a few weeks of captopril treatment.

All patients were hospitalized during the first week of captopril therapy in order to ensure the safety of the treatment. The trial took place over a period of 6 months. Captopril treatment was initiated at the dose of 6.5 mg b. d., which was increased stepwise to a maximum of 50 mg t. d. s. after 6 weeks. During the remaining study period, dose of the captopril was kept constant. Blood pressure, various biochemical tests and cell cation levels were estimated before com-

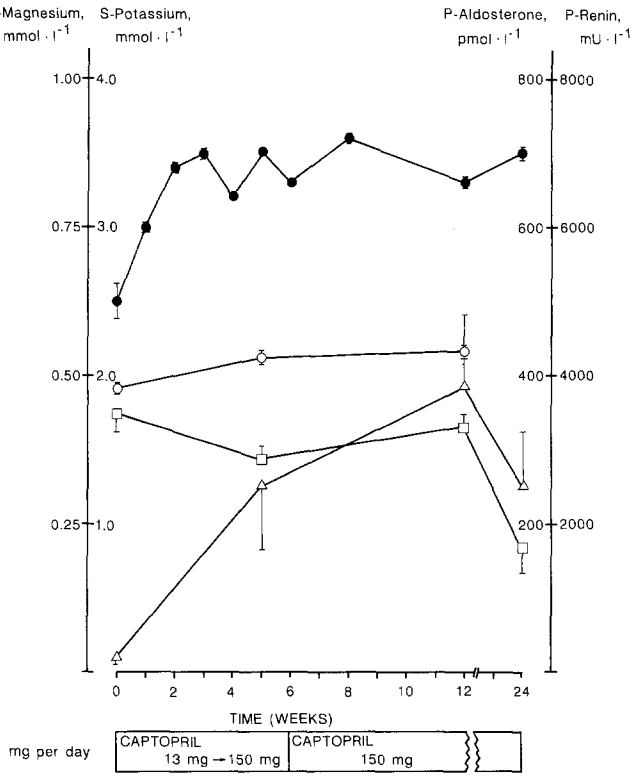

Fig. 1. Serum potassium and magnesium, and plasma aldosterone and renin in four subjects with Bartter's syndrome before and during treatment with captopril. Mean ± SD. S-Potassium (●), S-Magnesium (○), P-Aldosterone (□), P-Renin (△)

mencement of captopril therapy and regularly thereafter as indicated.

Lymphocyte sodium and potassium content and ^{22}Na efflux were measured according to published methods [6, 7]. Aldosterone and renin were analysed by radioimmunological methods.

The investigation was performed in accordance with the principles of the Declaration of Helsinki, as judged by the local Scientific-Ethical Committee. Informed consent was obtained from all participating patients.

Results

Captopril was well-tolerated by the four patients entering the trial, and no adverse effect was recorded. In particular, there were no complaints of dizziness or syncope. All subjects remained normotensive (mean with (SD) 122 (7)/73 (5) mm Hg) during the trial.

Biochemically, all patients fulfilled the diagnostic criteria for Bartter's syndrome (Fig 1). Mean plasma potassium was 2.5 (range 2.2–2.7) mmol·l^{-1}, plasma renin and aldosterone averaged 217 (80) mU·l^{-1} (reference value 10–77 mU·l^{-1}) and 347 (48) pmol·l^{-1} (reference values < 470 pmol·l^{-1}), respectively, and all subjects were moderately magnesium depleted, with a mean plasma level of 0.48 (0.03) mmol·l^{-1} (reference value 0.7–1.1 mmol·l^{-1}).

During captopril therapy the potassium level increased within two weeks to a mean of 3.4 (0.1) mmol·l^{-1}. This remained virtually unaltered throughout the study, despite the increments in the dose of captopril. Of the 4 patients, 3 who had suffered from fatigue became asymptomatic. This changes was associated with a slight increase in plasma magnesium but normal values were not attained. As expected, plasma renin was substantially increased, while plasma aldosterone was more than halved.

The results of the cell analyses are summarized in Fig 2. There was a substantial increase in mean (SD) lymphocyte sodium content from 14.90 (3.29) to 22.59 (6.33) mmol·l^{-1}. No changes in cell potassium content was observed. A slight increase in the total ^{22}Na-efflux rate constant was observed during captopril therapy, which was due to enhancement of the ouabain-resistant component.

Discussion

All efforts in the treatment of Bartter's syndrome are aimed at normalizing the serum potassium level. Oral potassium supplementation has proved ineffective, because most patients react by a proportionate increase in renal potassium excretion. Concomitant administration of an aldosterone antagonist, e.g. spironolactone [8], or a prostaglandin synthetase inhibitor, e.g. indomethacin, leads to a sustained but modest rise in serum potassium [9], and gives relief of symptoms in some patients.

The present investigation has shown that treatment with captopril, an angiotensin converting enzyme inhibitor, is associated with a substantial increase in plasma potassium and relief of hypokalaemia-related symptoms. These findings confirm those by other investigators, who have used captopril alone [10, 11] or in combination with an aldosterone antagonist [8], but are in contrast to a study in which captopril failed to increase serum potassium in 3 patients [12]. Administration of the ACE-inhibitor enalapril in the rather low dose of 10 mg/d to patients with Bartter's syndrome has led to almost normal serum potassium values [13, 14].

In the present study the effect of captopril persisted during the treatment period, in that no patients had a plasma potassium below 3.0 mmol/l. The maximum effect was achieved within 2–3 weeks with the modest dose of captopril of 6.5 to 12.5 mg b.d. No additional therapeutic benefit was obtained on further raising the captopril dose.

The normalizing effect of captopril on serum potassium is presumably not a consequence of a direct interaction between captopril and the electrolyte transport systems. No major change in lymphocyte cation regulation was found, except for an increase in cell sodium content [15]. This is in accordance with in vitro studies on the influence of captopril on dog kidney epithelial cells [17]. At therapeutic levels it has no effect on Na^+, K^+, Cl-cotransport, nor on the Na^+, K^+-ATPase activity. The increase in cell sodium content during treatment might be explained by the fact that lymphocytes isolated from Bartter's patients are characterized by an increased number of Na^+, K^+-pump sites due to chronic hypokalaemia [15]. As there is an increase in serum potassium during treatment the number of pump sites should return to normal, thus reducing the stimulating effect of physiological potassium concentrations as dictated by the methodology.

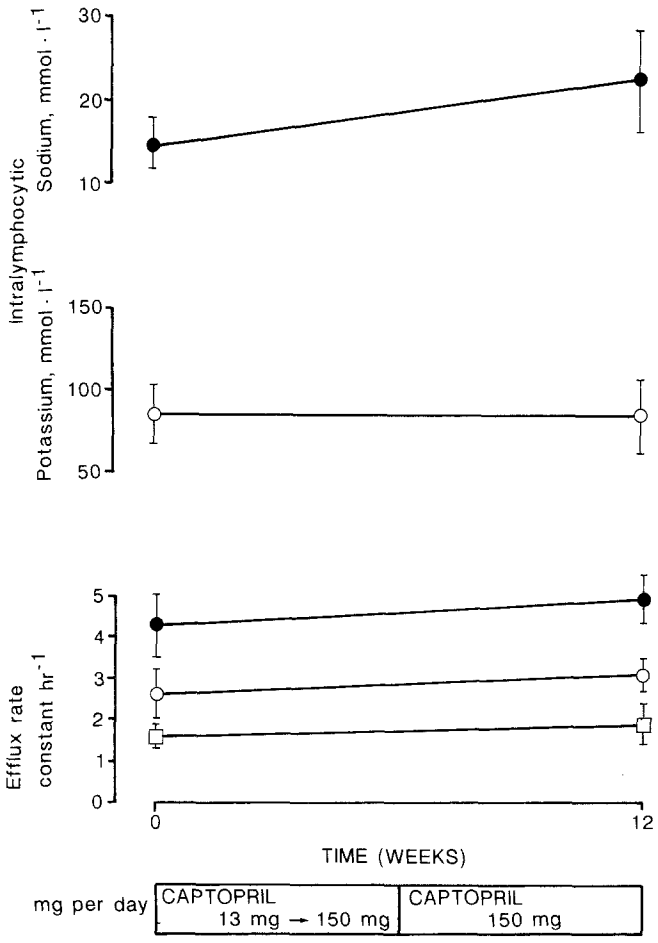

Fig. 2. Intralymphocytic sodium and potassium concentrations and sodium efflux rate constants. Total efflux rate constant (●), ouabain sensitive efflux rate constant (○) and ouabain resistent efflux rate constant (□) in four subjects with Bartter's syndrome before and during treatment with captopril. Mean ± SD

Whether the beneficial effect of captopril in Bartter's syndrome involves interference with the renin-aldosterone axis is questionable. Since captopril, even at high doses, leads only to partial correction of potassium depletion, it is reasonable to assume that other pathobiochemical processes than increased aldosterone production may contribute to renal potassium loss [3, 5]. It has been debated whether disturbances of volume regulation may contribute to the pathophysiology of Bartter's syndrome [2]. Some investigations have indicated a reduction in extracellular fluid volume followed by hyperaldosteronism as a secondary event [16]. The present results are against this hypothesis. If Bartter's patients were to be volume depleted, the natriuretic effect of captopril would inevitably lead to hypotension.

The pathobiochemical mechanisms underlying Bartter's syndrome remain to be clarified. However, captopril given in small doses has proven to be an effective tool in handling its hypokalaemic conditions.

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Dr. N. A. Klitgaard
Department of Clinical Chemistry
Odense University Hospital
Sdr. Boulevard 29
DK-5000 Odense C
Denmark