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Captopril induces correction of postrenal transplant erythremia

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Abstract. Kidney transplant patients may develop post-transplant erythremia (PTE), and in order to avoid thromboembolism venesection, anticoagulation and native kidney removal have been suggested. We propose captopril as an alternative therapy for PTE. Seven hypertensive PTE patients, aged 42 ± 10 years with stable renal function, were investigated to exclude primary or secondary polycythemia. All patients manifested true erythrocytosis [red blood cells (RBC) mass > 20% of predicted level] with concomitant increases in hematocrit and hemoglobin levels. Captopril was introduced in gradually increasing doses up to 75 mg/day under careful monitoring of blood pressure and renal function. Weekly follow-up was arranged to evaluate drug efficacy. After captopril, a significant reduction with normalization of the RBC mass (42 ± 4 vs 31 ± 5 ml/kg; $P < 0.005$) was observed. The RBC counts and hematocrit and hemoglobin levels also decreased. One patient had recurrent erythrocytosis after captopril withdrawal. Captopril may be a simple, effective, and non aggressive treatment for postrenal transplant erythremia.

Key words: Erythremia, post-transplantation – Captopril, erythremia

In the course of kidney transplantation, 6%–17% of all patients may develop post-transplant erythremia (PTE) [21]. Various etiological factors have been suggested to explain the pathogenesis of PTE [1, 2, 5, 10, 13, 15, 17, 20]. However, its cause remains obscure [21]. It seems that PTE is a transient and self-limiting phenomenon that, nevertheless, requires careful attention because of thromboembolic occurrences [19, 21]. Certain authors treat PTE by venesection, anticoagulation therapy, or native kidney removal [13].

In this paper, we report the results of a prospective study carried out in seven kidney transplant patients with PTE who were treated with captopril. We were encouraged by the well-documented property of angiotensin-converting enzyme (ACE) inhibitors to produce anemia in chronic renal failure (CRF) [14] and hemodialyzed patients [12], and by coincidental correction of PTE in two of our hypertensive PTE patients receiving captopril.

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Patients and methods

Patients

Seven Caucasian PTE patients (6 males, 1 female) with a mean age of 42 ± 10 years were investigated. Bone marrow analysis showed no primary proliferative polycythemia. Clinical and biological features, arterial blood gases, pulmonary function tests, and ultrasound examinations failed to detect the usual underlying etiological factors of secondary polycythemia. Patients had stable renal functions (serum creatinine 139 ± 29 μmol/l) and no hepatic dysfunction.

All patients manifested true erythrocytosis as evidenced by increased red blood cell (RBC) masses that were more than 20% (range 20%–72%) of the predicted level shown in a blood volume chart [16]. There was a concomitant increase in hematocrit (Hct; males > 52%, females > 47%) and hemoglobin (Hb; males > 18 g/dl, females > 16.5 g/dl) levels.

Table 1 summarizes the characteristics of patients. Original renal diseases were of different types. No patient had adult polycystic kidney disease. There was no nephrectomy. The onset of PTE varied from 6.4 to 28.1 months after renal transplantation. Erythrocytosis lasted for 1 to 31.1 months before this study, without showing PTE-related thromboembolic complications.

All patients were hypertensive for at least 3 months before captopril; three of them required renal graft arteriography showing no graft artery stenosis. Antihypertensive treatment consisted of calcium and β-blocking agents, which were modified after captopril in only two patients: in one, the β-blocker was reduced, and in the other, the Ca^{++} blocker was increased. No patient received diuretics. Immunosuppression consisted of either cyclosporin A (CyA) alone ($n = 4$) or CyA combined with 10 mg prednisolone ($n = 3$).

Therapeutic trial

After informed consent, oral captopril was administered at an initial dose of 6.25 mg and was gradually increased to 75 mg (25 mg × 3) per day starting on the 3rd day, with frequent monitoring of blood pressure (BP) and renal function. Patients were asked to avoid any situ-

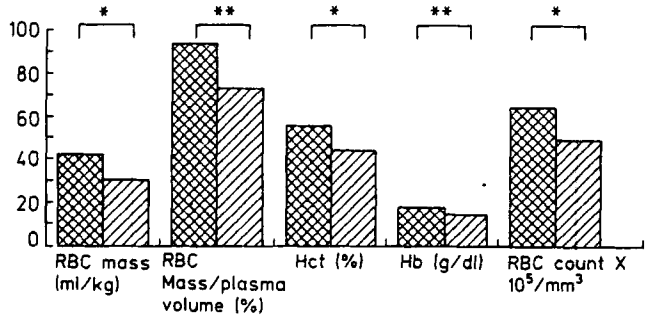

Fig. 1. Effect of captopril in postrenal erythremia. ▩ Before captopril, ▨ after captopril. * $P < 0.005$; ** $P < 0.01$

ation that might lead to dehydration. Smoking habits and body weight remained the same during follow-up.

Laboratory tests

Weekly follow-up was performed in an outpatient situation to determine the following biological parameters by standard laboratory methods: RBC count, Hct, Hb, serum creatinine, blood urea, serum electrolytes, natriuresis, and cyclosporin trough whole blood level (RIA monoclonal-specific, BAXTER kit). RBC mass, serum erythropoietin (EPO), peripheral renin activity (PRA), serum aldosterone, and serum iron were determined two to three times during the study period (range 1.5–6.8 months).

Blood volume determination was measured using ^{99}Tc-labelled RBC and ^{131}I-labelled human serum albumin. Serum EPO levels were measured by radioimmunoassay with the use of recombinant human EPO as tracer and immunogen.

Statistical analysis was done using the Wilcoxon rank-sum test for paired values. Results are expressed as mean ± SD.

Results

Figure 1 shows a significant reduction of PTE with normalization of RBC mass (42 ± 4 vs 31 ± 5 ml/kg; $P < 0.005$) under captopril. RBC count (64.9 ± 3 × $10^5/mm^3$ vs 49.8 ± 9 × $10^5/mm^3$; $P < 0.005$), Hct (56.4% ± 4.6% vs 44.7% ± 5%; $P < 0.005$), and Hb (18.1 ± 1.5 vs 15 ± 1.6 g/dl; $P < 0.01$) were also reduced significantly. The reduction of these hematological parameters without leukothrombocytopenia began in the 1st week of the study. Persistent decreases in Hct and Hb under captopril were observed in successive weeks, reaching normal levels within about 17 ± 15 days (Table 1). The ratio of RBC mass to plasma volume also decreased significantly (94% ± 15% vs 73% ± 19%; $P < 0.01$; Fig. 1). After 6 weeks, one patient (no. 3) showed recurrent erythrocytosis because captopril was withdrawn due to acute reversible renal failure related to dehydration.

The percentage of RBC mass reduction and the normalization of the hematological parameters were not related to the duration of captopril treatment (Table 1). The serum erythropoietin (EPO) level was 23 ± 9 mU/ml before captopril and decreased nonsignificantly to 18.6 ± 4 mU/ml after captopril (Table 2). However, these values were within our normal laboratory range (16–26 mU/ml determined in 17 healthy subjects).

Table 2 shows a significant decrease in diastolic BP (94 ± 7 vs 82 ± 8 mm Hg; $P < 0.01$) under captopril. Systolic BP, serum creatinine, blood urea nitrogen (BUN) creatinine, serum potassium, serum iron, and natriuresis showed no differences in pre- and post-captopril values. As there was no alteration in renal function, we retained the same maintenance oral CyA doses (3.24 ± 0.56 mg/kg), in spite of a significant decrease in CyA trough whole blood levels (202 ± 74 vs 150 ± 63 ng/ml; $P < 0.01$) within the therapeutic range. Supine PRAs were significantly increased, with a concomitant decrease in serum aldosterone, as may be expected after captopril. Similar but nonsignificant variations were observed in orthostatic measurements of these parameters. The mean arterial pressure changes were variable in different patients and do not follow the changes in hematological parameters during the study period.

Discussion

In this prospective study, we confirm captopril-induced reduction of post-transplant erythremia (PTE) was we had observed in our preliminary experiences with two PTE patients receiving captopril for uncontrolled hypertension. The RBC mass, as well as Hct and Hb levels and RBC count, returned to normal levels after administration of captopril. In order to avoid interference with the results, no therapeutic changes were allowed during the course of this study; smoking habits and body weight remained unchanged. This effect of captopril was observed as early as the 1st week and persisted throughout the trial period in all patients except one, who had recurrent erythrocytosis after captopril withdrawal. The rate of reduc-

Table 1. Characteristics of patients. PTE, Post-transplant erythremia; IgA N, IgA nephropathy; AS, Alport's syndrome; RA, renal amyloidosis; CRF, sudden chronic renal failure; Ph GN, proliferative hypocomplementemic glomerulonephritis; MGN, membranous glomerulonephritis

Patient	Sex/age (years)	Original renal diseases	Onset of PTE (months)	Duration of PTE state (months)	Follow-up under captopril (months)	Correction of PTE (days)	Percentage of RBC mass-reduction
1	M/42	IgA N	16.6	1.6	1.5	45	42
2	M/50	AS	25.6	4.5	1.5	9	20
3	M/58	RA	6.4	2.9	1.5	15	9.5
4	M/43	CRF	6.7	8.6	5.4	8	19
5	M/27	AS	7.2	1	1.5	5	12.4
6	M/37	Ph GN	23.2	24.9	4.6	30	31.6
7	F/36	MGN	28.1	31.1	6.8	7	49

Table 2. Biological data of patients before and after captopril treatment. Data are expressed as mean ± SD. *$P < 0.05$; **$P < 0.01$

Mean values	Before captopril	After captopril
Blood pressure (mm Hg)		
Systolic	147 ± 16	140 ± 20
Diastolic	94 ± 7	82 ± 8**
Serum creatinine (μmol/l)	139 ± 29	138 ± 20
Blood urea nitrogen creatinine (%)	7.44 ± 1.8	7.34 ± 1.1
Serum potassium (mmol/l)	4.6 ± 0.4	4.7 ± 0.2
Serum iron (pmol/l)	12.8 ± 5.6	13.5 ± 5.9
Natriuresis (mmol/24 h)	139 ± 51	123 ± 43
Ciclosporinemia (ng/ml)	202 ± 74	150 ± 63**
Peripheral renin activity (ng/ml per hour)		
Supine	1.82 ± 1.4	3.39 ± 2.2*
Standing	2.23 ± 1.3	2.32 ± 0.73
Serum aldosterone (pg/ml)		
Supine	172 ± 64	102 ± 78*
Standing	261 ± 97	200 ± 107
Erythropoietin (mU/ml)	23 ± 9	18.6 ± 4

tion of the RBC mass and other hematological parameters had no correlation with the duration or dose of captopril, suggesting individual variations in the efficacy of captopril. However, the duration of PTE correction might have depended on the initial values of hematological parameters when captopril was first introduced.

The mechanism of captopril-induced PTE correction may find its explanation in the already known anemia-worsening property of ACE inhibitors in chronic renal failure (CRF) patients [12, 14]. As angiotensin-II (A-II) is known to exert a direct effect on EPO production [7], a reduction of A-II by ACE inhibitors has been suggested to aggravate anemia. In our patients, correction of erythremia may also have been a result of A-II reduction due to the blockade of the renin-angiotensin-aldosterone-system by captopril, as observed by the relative increase in PRA associated with a decrease in serum aldosterone.

On the other hand, RBC mass elevation has been reported in the course of hypertension related to renal tissue hypoxia [9]. Although no precise etiological factors are available, multiple pathological events have been suggested as causes of PTE, among them graft rejection [2, 15], renal graft artery stenosis [1, 17], diseased native kidneys [5, 13], and treatment with CyA [10, 20]. These pathological circumstances may cause renal ischemia, resulting in primary stimulation of EPO production and, hence, PTE. Captopril, having the property to increase renal blood flow and postglomerular vasodilatation, may improve renal ischemia and reduce EPO production, as seen with ACE inhibitors in CRF patients [12, 14]; in this way, captopril may induce PTE correction. However, the renal vasodilatory effects of ACE inhibitors may be true for renal grafts as well as for diseased native kidneys.

EPO levels were not significantly high in our patients and they remained within the normal range after captopril. Some authors have suggested that once initiated, erythropoiesis continues with lower or normal levels of EPO [18] and that PTE is not invariably associated with elevated serum EPO levels [22]. Yet, increased EPO sensitivity of erythropoietically determined stem cells may exist in the post-transplant period [11]. These hypotheses may explain the difficulty of demonstrating evidence of EPO dependence in PTE. In fact, by its renal vasodilatory action, captopril may act on the heart of "EPO dysregulation", thus inhibiting stimulation of erythrocytosis.

Simultaneous overproduction of EPO and renin has been reported in a patient with Bartter's syndrome [6]; both EPO and renin activities are reported to be increased in renovascular hypertension [3]. These findings suggest the involvement of closely related mechanisms to produce both hormones. Renin substrate (angiotensinogen) has been proposed as a likely precursor of EPO because of its chemical similarities and comparable immunological and biological properties [8]. In addition to the antihypertensive property in renin-dependent patients, ACE inhibitors may also be effective in EPO dysregulation in PTE. The mean arterial pressure changes did not follow the rate of decrease in the hematological parameters during our study period, and this may be due to a differential effect of captopril on BP and PTE. Yet, our patients were all hypertensive and captopril reduced arterial BP – especially diastolic BP – as it reduced the RBC mass.

We observed relative safety in the use of captopril in our patients receiving CyA. There was no hyperkalemia and no graft dysfunction. CyA-induced sodium and water retention prevents easy dehydration and thus may be beneficial in this regard [4]. In our patients there was neither weight gain nor volume contraction, as shown by unchanged BUN/creatinine ratios. In comparison with other proposed PTE treatments like venesection and native kidney removal, captopril is a rather simple and nonaggressive approach. However, long-term prescription of ACE inhibitors for patients with a solitary functioning kidney requires great attention, and patients must avoid dehydration.

Lastly, we observed a significant decrease in CyA trough whole blood levels after the introduction of captopril. As no pharmacological interaction is known between captopril and CyA, this may reflect a loss of intraerythrocytic CyA due to RBC mass reduction. Further studies are needed to confirm these data.

We used 75 mg of captopril per day and found that the correction of PTE was accomplished within a short period. The question now arises: what is the effective minimal and optimal dose of captopril to resolve PTE definitively without any recurrence, and how long should one keep patients under captopril? Will these patients develop anemia in the long run? Sufficient follow-up of these patients may answer these questions in the future.

In conclusion, we demonstrate in this study that captopril may be a simple, safe, and nonaggressive therapy for postrenal transplant erythremia. However, one must bear in mind the possible hazards of such a therapy in the solitary kidney.

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