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Original Article

The impact of withdrawing ACE inhibitors on erythropoietin responsiveness and left ventricular hypertrophy in haemodialysis patients

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Abstract

Background. Angiotensin-converting enzyme (ACE) inhibitors have the capability of decreasing left ventricular mass index (LVMI) in chronic haemodialysis (HD) patients. On the other hand, recent reports provide conflicting information regarding the impact of ACE inhibitors on responsiveness to recombinant human erythropoietin (rHuEpo), and there are no data about the effect of withdrawing ACE inhibitors both on rHuEpo response and LVMI in HD patients.

Methods. ACE inhibitors were switched to another antihypertensive medication in 23 out of 68 patients in our HD unit who were receiving both rHuEpo and an ACE inhibitor for more than 1 year. Blood pressure at the pre- and post-dialysis phases, haematocrit levels and rHuEpo doses were determined at the end of the first and of the third years, and the LVMI was determined at the end of the third year. Statistical analyses were done in 15 patients in whom the study could be completed.

Results. The mean ($\pm$SD) haematocrit level was increased from $26.3 \pm 6.4\%$ to $29.8 \pm 6.3\%$ at the first year ($P < 0.05$), and to $29.4 \pm 6.5\%$ at the third year ($P < 0.05$ *vs* before), while the mean dose of rHuEpo was decreased from 208.3 ± 99.0 UI/kg/week to 141.0 ± 91.8 at the first year ($P = 0.01$), and to 141.4 ± 81.0 at the third year ($P = 0.01$ *vs* before). Administration of rHuEpo had been stopped in two patients at the end of the first year. The mean blood pressure level and the mean LVMI were not changed ($P > 0.05$ *vs* before). There were no significant changes in dialysis parameters, iron status, plasma renin activities, and levels of aldosterone, intact parathyroid hormone, aluminum and erythropoietin.

Conclusion. The findings of this small uncontrolled study indicate that withdrawl of ACE inhibitors in hypertensive chronic HD patients receiving rHuEpo may result in an increase in haematocrit level, and a decrease in dose of rHuEpo without any significant changes in the blood pressure level and LVMI. Controlled prospective studies are needed to clarify this issue.

Key words: ACE inhibitors; anaemia; erythropoietin; haemodialysis; hypertension; left ventricular hypertrophy

Introduction

The introduction of recombinant human erythropoietin (rHuEpo) into clinical practice has been a very important improvement for the management of anaemia of end-stage renal disease (ESRD) [1,2]. However, the dose of rHuEpo required to correct anaemia varies among the patients, and some can be unresponsive in spite of applying very high doses. The common causes for inadequate response to rHuEpo are iron deficiency, infection and inflammation, osteitis fibrosa, aluminium toxicity, folate or vitamin B12 deficiency, inadequate dialysis, and malnutrition [3,4]. Nevertheless, the reason for incomplete response to rHuEpo is not completely clear, as some patients lacking these factors can also be unresponsive to rHuEpo.

Left ventricular hypertrophy (LVH) is quite frequent in chronic haemodialysis (HD) patients, and hypertension and anaemia are the major predictors of this complication [5–7]. Angiotensin-converting enzyme (ACE) inhibitors are shown to induce regression of LVH in patients with essential hypertension [8,9], chronic renal failure [10], and ESRD [11]. In addition, hypertension in HD patients has been shown to be successfully treated by this class of drugs without any significant untoward event [12]. Accordingly, ACE inhibitors seem to be drugs of choice for the treatment of both LVH and hypertension in chronic HD patients.

In experimental and clinical studies, ACE inhibitors have been shown to cause anaemia [13,14]. Hence, an initial concern that ACE inhibitors would worsen the anaemia of ESRD came up. More recent reports, however, provide conflicting information about this issue: some reports suggested that there was neither an increase in doses of rHuEpo nor a decrease in haemato-

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crit by ACE inhibitors [15–17], whereas the others concluded that this class of drugs did inhibit the action of rHuEpo [18,19].

As far as our knowledge is concerned, there is no report evaluating the impact of withdrawl of ACE inhibitors both on the treatment of anaemia and LVH in HD patients. Therefore, we designed the present study to investigate the effects of substitution of ACE inhibitor by another antihypertensive medication on rHuEpo responsiveness, blood pressure control, and left ventricular mass index (LVMI) in hypertensive chronic HD patients.

Subjects and methods

Twenty-three out of 68 patients in our HD unit were being administered both rHuEpo and an ACE inhibitor for more than a year (i.e. enalapril 10–40 mg/day, 19 patients; captopril 25–75 mg/day, three patients; and perindopril 2 mg/day, one patient). After a 3-month period for the basal evaluations, ACE inhibitor was switched to another antihypertensive medication in all patients (i.e. amlodipine 5–10 mg/day in 12 patients, felodipine 5 mg/day in six patients, and doxazosin 4–8 mg/day in five patients). During the first year of the study, four patients received renal allografts, three started continuous ambulatory peritoneal dialysis, and one patient died from an untreatable pulmonary infection. Hence, those eight patients were excluded from the study. None of the remaining 15 patients had haematological diseases, active untreated infections, malignancies or other causes of inflammation.

All patients were dialysed with a single-use cellulosic cuprophane capillary membrane three times a week (12 h/week), using bicarbonate dialysate bath. During HD, all patients were ultrafiltrated to achieve their estimated dry weight. Ultrafiltration volume (as per cent of body weight), and Kt/V(urea) values according to Daugirdas [20] were calculated monthly. Blood pressure measurements were done before and after each HD session. Administration of rHuEpo was done through subcutaneous route at the end of the HD session, and the doses were adjusted monthly. A patient was defined as being resistant to rHuEpo if a haematocrit level of 30% could not be achieved despite applying a rHuEpo dose above 200 UI/kg/week [18]. All patients were given oral iron and calcitriol. Intravenous iron infusion was used as necessary [3].

The following laboratory evaluations were done in all patients: haematocrit and routine biochemistry (monthly); transferrin saturation, and ferritin (every 3 months); vitamin B12, folate, intact parathyroid hormone (iPTH), and aluminum (every 6 months); and plasma renin activity, aldosterone, and erythropoietin (at the end of the first and third years). Blood samples for the evaluations were taken immediately after the HD session.

Two-dimensional and M-mode echocardiography were performed just before, and 3 years after, the withdrawing of the ACE inhibitor, using Hewlett Packard Sonos 1000, with a 2.5-MHz transducer. All patients were examined in the left lateral decubitus position by a single experienced echocardiographer, who was blind to the results of the other study parameters evaluated. All measurements were made according to the American Society of Echocardiography guidelines [21]. M-mode measurements included interventricular septal thickness, left ventricular posterior wall thickness, left ventricular end-systolic diameter (LVESD), and left ventricular end-diastolic diameter (LVEDD). Left ventricular fractional shortening (FS) was derived from the formula of

$$(\mathrm{LVEDD}-\mathrm{LVESD}/\mathrm{LVEDD})\times 100\%.$$

Left ventricular mass was determined from M-mode measurements according to Devereux *et al.* [22], and indexed to body surface area to give LVMI.

Statistical analysis

For statistical analyses of haematocrit, rHuEpo dose, ultrafiltration volume, Kt/V(urea), and of the blood pressures, the averages of the last 3 months values of each period (i.e. under, and 1 and 3 years after the ACE inhibitor) were used. For the other parameters single measurements obtained just before, and at the end of the first and third years after weaning were used. To evaluate the data, Wilcoxon matched-pairs signed-ranks test was used. Unless stated otherwise, all data were reported as the mean $\pm$ SD. Two-tailed P values <0.05 were considered statistically significant.

Results

Demographic features of the patients and the relevant laboratory data are shown in Table 1. There were 10 men and 5 women, and the mean age was 33.7 ± 8.4 years (range 18–50 years). Causes of ESRD were chronic tubulointerstitial nephritis in six patients, chronic glomerulonephritis in five patients, and unknown in four patients. The mean duration under HD treatment at the beginning of the study was 68.5 ± 25.7 months (range 24–120, median 60 months). Mean Kt/V(urea) value under an ACE inhibitor was 1.17 ± 0.18, and those at 1 and 3 years after the weaning of the drug were 1.18 ± 0.22 and 1.23 ± 0.26, respectively ($P>0.05$ *vs* before).

Nine patients (60%) were resistant to rHuEpo at the baseline. Haematocrit levels in 13 patients (86.7%) started to increase 3 months after the withdrawl of ACE inhibitor. The mean haematocrit level was increased from $26.3\pm6.4\%$ to $29.8\pm6.3\%$ at the first year ($P<0.05$), and to $29.4\pm6.5\%$ at the third year ($P<0.05$ *vs* before). Dose of rHuEpo was decreased in 11 patients (73.3%) after the substitution. The mean dose of rHuEpo was decreased from 208.3 ± 99.0 UI/kg/week to 141.0 ± 91.8 ($P=0.01$) at the first year, and to 141.4 ± 81.0 ($P=0.01$ *vs* before) at the third year. Moreover, rHuEpo had been stopped in two patients at the end of the first year.

There were no significant changes with regard to body weight, ultrafiltration volume, transferrin saturation, ferritin, vitamin B12, folate, iPTH and aluminum, either at the end of the first or of the third years ($P>0.05$ *vs* before). In addition, plasma renin activities, aldosterone, and erythropoietin levels were not changed after the withdrawl of ACE inhibitor ($P>0.05$ *vs* before).

Blood pressure was well controlled in 12 patients at the baseline, and no patients exhibited aggravation of hypertension after the ACE inhibitors were stopped. Similarly, all 13 patients having LVH at the baseline

Table 1. Demographic features of the patients and the relevant laboratory data

15 patients, (10 male, 5 female)	Under ACE inhibitor	After the withdrawing of ACE inhibitor	
		First year	Third year
Age (years)	33.7 ± 8.4		
HD duration (months)	68.5 ± 25.7		
Kt/V (urea)	1.17 ± 0.18	1.18 ± 0.22	1.23 ± 0.26
Ultrafiltration volume (%)	4.8 ± 1.3	5.3 ± 1.6	5.3 ± 1.4
Haematocrit (%)	26.3 ± 6.4	29.8 ± 6.3	29.4 ± 6.5
rHuEpo dose (UI/kg/week)	208.3 ± 99.0	141.0 ± 91.8	141.4 ± 81.0
Transferrin saturation (%)	33.7 ± 11.1	32.4 ± 8.5	32.1 ± 9.6
Ferritin (ng/ml)	187.0 ± 165.6	207.6 ± 262.4	215.0 ± 155.3
Vitamin B12 (pg/ml)	773.5 ± 310.8	876.2 ± 227.5	633.1 ± 522.9
Folate (ng/ml)	26.2 ± 13.2	29.4 ± 15.0	30.4 ± 25.4
iPTH (ng/dl)	333.6 ± 250.7	451.3 ± 447.1	375.8 ± 272.8
Aluminum (μg/l)	17.5 ± 9.1	26.0 ± 22.1	25.8 ± 24.7
PRA (ng/ml/h)	2.6 ± 2.5	2.5 ± 2.1	2.4 ± 1.8
Aldosterone (ng/dl)	84.1 ± 107.1	66.9 ± 82.3	49.5 ± 66.2
Erythropoietin (mIU/ml)	28.3 ± 22.8	28.5 ± 32.0	30.1 ± 42.0

still exhibited LVH at the end of the study. The mean LVMI at the end of the third year (241.8 ± 71.0 g/m^2) was the same as that at the beginning (236.7 ± 57.3 g/m^2), ($P > 0.05$) (Table 2). The mean blood pressure levels both at the pre-dialysis and post-dialysis phases were not changed after the withdrawl of ACE inhibitor ($P > 0.05$ *vs* before). On the other hand, both before and after discontinuing of the drug, systolic blood pressure levels were found to be decreased significantly after the HD session ($P < 0.05$ *vs* pre-dialysis), whereas reductions in diastolic blood pressure levels were not statistically significant ($P > 0.05$).

Discussion

Hypertension and anaemia are the major predictors of cardiovascular disease in patients with ESRD [5–7]. ACE inhibitors are shown to control hypertension effectively [12], and to have the capability of decreasing LVMI in patients with various diseases including ESRD [8–11]. On the other hand, negative implications of ACE inhibitors in erythropoiesis, if present, would be opposite to their desirable effects on LVH. In the present study, LVMI was not increased 3 years after the withdrawl of ACE inhibitor, probably as a consequence of the better control of anaemia [23]. However, it may be speculated that if the ACE inhibitors had been continued and the haematocrit had been kept at the same level there would have been a further reduction in LVMI. Controlled prospective studies are needed to clarify this point.

In this study, either a dihydropyridine calcium antagonist (amlodipine or felodipine) or a peripheral alpha 1-adrenergic antagonist (doxazosin) substituted the ACE inhibitor. Both of these classes of drugs may achieve regression of LVH [24,25]. Moreover, there are no data about their negative effects on rHuEpo responsiveness. During the study period, blood pressure was kept at the same level without aggravation of hypertension in any patients, and LVMI remained stable. However, the low number of patients included in the follow-up prevents us establishing definitive conclusions about the long-term impact of antihypertensive drugs, different from ACE inhibitors, on rHuEpo responsiveness and LVMI.

Participation of the renin–angiotensin system in

Table 2. Blood pressure levels and LVMI under and after the withdrawing of ACE inhibitor

	Under ACE inhibitor	After the withdrawing of ACE inhibitor	
		First year	Third year
Pre-dialysis BP (mmHg)			
Systolic	146.7 ± 20.3	147.0 ± 19.5	140.0 ± 11.8
Diastolic	89.3 ± 12.1	88.0 ± 17.3	83.7 ± 6.4
Post-dialysis BP (mmHg)			
Systolic	135.7 ± 24.0	132.0 ± 20.8	131.3 ± 15.8
Diastolic	82.0 ± 13.5	79.0 ± 16.1	81.0 ± 8.1
LVMI (g/m^2)	236.7 ± 57.3		241.8 ± 71.0

erythropoiesis has long been recognized. Angiotensin II directly stimulates erythropoietin production *in vivo* [26,27], and induces the growth of early erythroid progenitors *in vitro* [28]. ACE inhibitors and angiotensin II type 1 receptor antagonists have been shown to decrease erythropoietin levels in animals [27,29], in renal transplant recipients with or without post-transplant erythrocytosis [30–32], and in uraemic patients [33]. In addition production of interleukin-12 [34] and levels of IGF-1 [32], cytokines known to induce erythropoiesis, were shown to be reduced by ACE inhibitors. Convenient with these observations, it has been demonstrated by several studies that both ACE inhibitors and angiotensin II type 1 receptor antagonists might contribute to anaemia or to a decrease in haemoglobin/haematocrit levels in animals [13,29], in patients with chronic renal failure [35], with renal allografts [30–32], and in patients under HD treatment [14]. Moreover, it has been shown that the use of ACE inhibitors might result in an increase in rHuEpo dose to maintain the desired haematocrit levels in dialysis patients [18,19,36]. Nevertheless, there are some reports suggesting a poor response to rHuEpo was not the case with ACE inhibitors [15–17]. This discrepancy among the reports may arise from the different drug doses administrated [19], from ACE gene polymorphism by which the renin–angiotensin system activation may be different from patient to patient (so that inhibition may result in different consequence) [9], or from other unknown mechanisms.

We have previously demonstrated in a cross-sectional study that ACE inhibitors may cause rHuEpo unresponsiveness in HD patients [18]. In the present study, we have shown that at the end of the first year of the withdrawl of ACE inhibitor, haematocrit levels were increased while rHuEpo doses were decreased, and that these findings were stable at the end of the third year. These results correlate with the results of a recent study done by Albitar *et al.* [19], in which enalapril was shown to increase rHuEpo requirement in HD patients. In that study, the mean rHuEpo dose in patients given enalapril, showed a return to baseline values 4 months after discontinuing the drug. Although we could not demonstrate the exact mechanism for a better response to rHuEpo after discontinuing of the ACE inhibitor, it seems different from the effects on endogenous erythropoietin levels since those at the beginning were the same with both at the first and at the third years. Serum erythropoietin levels had not been evaluated in the Albitar *et al.* study [19]. On the other hand, Julian *et al.* had achieved a decrease in haematocrit levels with losartan, an angiotensin II type 1 receptor antagonist, in patients with post-transplant erythrocytosis, and has reported that after withdrawal of the drug haematocrit had been increased without any change in serum erythropoietin [31].

We acknowledge that the present study has several limitations. First, we studied a relatively small number of patients, but the main reason was our belief that ACE inhibitors cause rHuEpo unresponsiveness [18]. We generally do not prescribe this class of drugs as the first step in our hypertensive HD patients receiving rHuEpo. Secondly, some of our patients had either low ferritin levels indicating that iron deficiency was present at least in part of our patients, or high iPTH levels, factors known to cause poor response to rHuEpo. However, these parameters were not changed during the study period, and the unique factor for a better response to rHuEpo was the weaning of the ACE inhibitor. Thirdly, it might be relevant to evaluate plasma renin activities, aldosterone, and erythropoietin levels by more sequential studies within the first year after substitution of the ACE inhibitors by other antihypertensive drugs. Although peripheral hormone levels do not necessarily reflect the exact activity at the tissue level, and renin–angiotensin system is affected by many factors, including salt and fluid intake, ultrafiltration, and drugs in HD patients; such an attempt could allow for the explanation of the mechanisms potentially involved in the recovery of rHuEpo responsiveness. Finally, neither the reason for incomplete response to rHuEpo, nor the mechanism for a better response after the withdrawing of the ACE inhibitors could be found in the present study. Unfortunately, there is currently no study evaluating all probable factors participating in erythropoiesis or rHuEpo response in HD patients. We think that further studies especially evaluating the impact of various cytokines [28,34,37,38] would help to solve this issue.

In conclusion, the withdrawl of ACE inhibitors in hypertensive chronic HD patients receiving rHuEpo may result in an increase in haematocrit level and a decrease in dose of rHuEpo without any significant changes in the blood pressure level and LVMI. We recommend that ACE inhibitors can be safely switched to another antihypertensive medication in HD patients if poor response to rHuEpo exists. However, as the present study is small and uncontrolled, the conclusions drawn need to be confirmed in a controlled prospective study.

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Editor's note

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