Successful long-term treatment of post-transplant erythrocytosis with losartan

K. Midtvedt, E. S. Stokke and A. Hartmann
Section of Nephrology, Medical Department B, National Hospital, Oslo, Norway

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Introduction

Erythrocytosis is a relatively common complication following renal transplantation [1–3]. The aetiology of post-transplant erythrocytosis (PTE) remains unclear. ACE inhibitors have emerged as a safe and efficacious treatment of PTE [4,5]. The ACE inhibitor lisinopril proved to be effective in the case reported, but had to be withdrawn due to hypotension. However, the PTE was successfully treated with an angiotensin II receptor antagonist, losartan. To our knowledge this is the first case report to demonstrate an effect of an angiotensin II antagonist on PTE, indicating that the effect of ACE inhibitors in PTE is possibly mediated via angiotensin II receptor blockade.

Case report

A 42-year-old woman had proteinuria recognized during her first pregnancy in 1982. The proteinuria persisted, but her serum creatinine value remained normal, also following a later pregnancy in 1984. A clinical diagnosis of CGN was given, but no biopsy was performed. The patient was lost to further follow-up until she presented with uraemic symptoms, and haemodialysis was started in April 1991. Due to HLA antibodies the patient was treated with repeated sessions of IgG adsorption (Excorim®, Gambro, Lund, Sweden), prednisolone and cyclophosphamide according to our transplant programme for HLA antibody-positive patients at that time [6]. Subsequently she was transplanted with a 1 DR mismatched necro-donor kidney in January 1992. Anti-lymphocyte globulin induction therapy was used as part of a quadruple immunosuppressive drug regimen. Long-term immnosuppression consisted of cyclosporine A, azathioprine and prednisolone.

She underwent two rejection episodes. Both were successfully treated, the first with i.v. methylprednisolone and OKT3, the second with i.v. methylprednisolone alone. Except for a subsequent CMV infection treated with 14 days i.v. gancyclovir, there were no further complications and the serum creatinine stabilized at a value of about 180 μmol/l.

Repeated haemoglobin values during the first month following transplantation averaged 10 g/dl. The haemoglobin values gradually increased and reached 17 g/dl in July 1992 with a haematocrit of 52%. Despite a relatively low blood pressure of 110/80 mmHg, lisinopril in a dose of 2.5 mg o.d. was started in September 1992 as treatment for her PTE. The treatment was efficient inasmuch as the haemoglobin values gradually declined, reaching 13.8 g% in February 1993. However, she complained of dizziness, a casual blood pressure of 90/70 mmHg was recorded, and the drug was discontinued at that time. A rise in haematocrit during the next 3 months to values over 50% led to repeated phlebotomies every 4–8 weeks (500 ml blood each session) to keep haematocrit under 50%, starting in June 1993. As thrombosis prophylaxis she received 160 mg acetylsalicylic acid o.d. Altogether 20 phlebotomies were performed from June 1993 to May 1995. White blood cell and platelet counts revealed values between 4 and 6 x 10^9/l and 150 and 200 x 10^9/l, respectively. Following the 2 years of repeated phlebotomies the iron saturation index (SeFe/TIBC x 100) was 19%, with a serum ferritin value of 17 μg/l. Serum erythropoietin (EPO) levels were consistently low: six measurements were below the detection limit for the analysis (<2 U/l) and two measurements were in the low normal range during repeated phlebotomies and during losartan treatment. Intact PTH serum values were moderately elevated and stable, averaging 10 pmol/l. Serum creatinine remained stable around 180 μmol/l and blood pressure remained normal (average 115/83 mmHg). Serum bilirubin, ASAT (SGOT), ALAT (SGPT), LD, gammaGT and alkaline phosphatase values remained within the normal range over the period studied.

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After informed consent was given, losartan treatment was started in June 1995 at a dose of 25 mg o.d. to evaluate a possible beneficial effect on PTE. The drug was well tolerated and the dose was increased to 50 mg o.d. in November 1995. From the start of losartan treatment to date (May 1996), no further phlebotomies have been performed, and the haematocrit values have remained in the range 38–44%. Losartan was withdrawn for 2 months (January/February 1996) due to episodes of dizziness when blood pressure was 102/60 mmHg. During these 2 months there was a rise in haematocrit from 38% to 44%, and losartan was reinstituted in a lower dose (25 mg o.d.). The lower dose was again well tolerated (blood pressure 117/80 mmHg, mean of five subsequent blood pressure recordings).

The effect of losartan on haemoglobin and haematocrit is shown in Fig. 1. The effects are clear-cut and may also be dose dependent. After cessation of therapeutic phlebotomies the iron saturation index (SeFe/TIBC x 100) increased from 19% to 25%, and the serum ferritin values from 17 μg/l to a median value of 50 μg/l. The patient’s general condition improved, and she was able to return to work.

Discussion

To our knowledge this is the first report on the efficacy of an angiotensin II (AII) antagonist (losartan) in the treatment of PTE. This case suggests that the well-known effect of ACE inhibitors in the treatment of PTE is possibly mediated via AII receptors.

Erythrocytosis is a common phenomenon following renal transplantation. The incidence ranges from 10% to 22% and it usually develops within 12–16 months after transplantation [1–3]. Our patient developed PTE over 6 months, and the need for phlebotomies remained high indicating a severe form of PTE. Deducted from the need for phlebotomy before treatment with losartan, a number of about 10 phlebotomies have been avoided during the observation period. The iron saturation index and iron stores, estimated from serum ferritin values, increased after cessation of phlebotomies ruling out iron deficiency as the reason for the successful control of PTE during losartan treatment.

Standard therapy in a transplant recipient with PTE should include elimination of all reversible components of polycythaemia. The suggestion that overproduction of EPO is the principal cause of PTE has resulted in an emphasis on decreasing EPO secretion. One option is bilateral native nephrectomy, which was not considered in our patient. Other treatment options, such as theophylline [7,8] and ketanserin treatment [9], may act via inhibition of EPO production. However, theophyllines are not as effective as ACE inhibitors, may have more side effects and also may interfere with the metabolism of other drugs [10].

The combination of PTE and low blood pressure observed in our patient is rather uncommon; on the contrary PTE generally carries a higher risk of hypertension, vascular accidents and vascular thrombosis because of increased blood viscosity [11,12]. It is possible that losartan, acting directly on the AII receptors, reduced PTE with tolerable effect on blood pressure, whereas the low dose of ACE inhibitor with a similar effect on the PTE could not be tolerated due to an additional hypotensive effect of bradykinins induced by the ACE inhibitor.

The aetiology of PTE remains unknown. Many
mechanisms have been postulated; a prevailing hypothesis has been an overproduction and excessive secretion of EPO in the native kidneys, the allograft or the liver [13,14]. Several studies have however shown undetectable plasma EPO levels [15–17] in PTE patients. Also, the inhibitory effect of ACE inhibitors on the production of red blood cells remains obscure. An effect of ACE inhibitors on EPO production has been indicated, but the findings are inconsistent, and the hypothesis has been challenged [4,18]. In the patient reported here, the serum EPO levels were consistently very low or in the lower normal range. Although the EPO values may still be high compared with the elevated haemoglobin values, the findings in our patient do not favour an effect of AII blockade (or ACE inhibition) via inhibition of EPO production. In a small open study on elderly patients with essential hypertension, losartan did not show a significant reduction in EPO concentrations [19].

We conclude that the angiotensin II receptor blocker losartan was safe and effective in the treatment of PTE. Further studies are obviously needed to establish the future role of angiotensin II blockers in the treatment of PTE.

References

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