The effect of angiotensin II receptor antagonist on the exogenous erythropoietin requirement of haemodialysis patients

Sir,

The effects of angiotensin converting enzyme inhibitors (ACEI) [1–3] and angiotensin converting enzyme receptor antagonists (AIIRA) [4,5] for correction of post-transplantation polycythaemia have now been described in several series. The mechanism of action is speculative, one presumption being the improvement in native kidney perfusion resulting in reduced endogenous erythropoietin production [6]. ACEI and AIIRA are commonly used in the management of systemic hypertension and of systolic left ventricular failure in dialysis dependent patients, and as a consequence the erythropoietic response to rHuEpo may be blunted. If this is true, could the mechanism relate to the reduction in their endogenous erythropoietin production? The effect of ACEI on the haemoglobin/haematocrit of haemodialysis patients on rHuEpo has been studied by several investigators with mixed conclusions [7–12]. Most reports were retrospective, none were blinded and the majority appeared not to account for the myriad of factors which may affect the response to rHuEpo administration. The effect of AIIRA had not been investigated at the commencement of our trial.

We performed a double blind, placebo controlled, prospective, cross-over study on the effect of AIIRA on erythropoietic response to rHuEpo involving 14 stable haemodialysis patients, seven males and seven females, on rHuEpo, who were clinically stable, with stable haemoglobin (> / = 10 g/dl), and constant rHuEpo dose. The exclusion criteria were chronic refractory iron deficiency (transferrin saturation <20%); excessive serum aluminium (> 30 mcg/l); excessive hyperparathyroidism (> 50 pmol/l); impending surgery with potential haemorrhage; chronic uncorrected blood loss or haemolysis; impending live renal transplantation; intolerance...
or allergy to ACEI or AIIRA. The subjects were randomized to receive daily either placebo capsule or 12.5 mg losartan for 1 week. In the absence of adverse drug reaction the 12.5 mg capsule was replaced with a 25 mg capsule, to be taken for the following 3 months. After a 2 week washout period a cross-over of the study drugs occurred for the subsequent 3 months, with the precautionary 12.5 mg losartan in the first week. All but one subject received 25 mg losartan daily throughout the study. Five subjects were prematurely withdrawn at various stages for reasons of: trial drug intolerance; gastro-intestinal haemorrhage; non-compliance; femoral fracture requiring surgery; and one subject received a renal transplant.

There were two measured parameters. The first was haemoglobin level, measured fortnightly, mid-week predialysis. The second was serum erythropoietin, measured at three points: prior to starting the trial drug; at the end of the first 3 months; and at the end of the second 3 months or at premature withdrawal from the study. The rHuEpo doses were maintained constant throughout the study. As the method of measurement did not discriminate between endogenously produced and exogenously administered erythropoietin, we had hoped that our measurements would reflect any fluctuations in the subjects’ endogenous erythropoietin production.

We found no statistically significant difference in the haemoglobin levels over time whilst the subjects were on losartan versus placebo (Figures 1–4). The serum erythropoietin results were somewhat variable (Table 1), and not surprisingly there was no statistically significant difference in the subjects’ levels whilst on losartan versus placebo.

There were several important aspects of our study design worthy of comment:

(i) The losartan dose was comparatively low. This was to avoid undue hypotension in otherwise stable patients.

(ii) The number of subjects was too small, as a consequence of the stringent exclusion criteria which were necessary to eliminate the multiple potential confounding factors. The

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### Table 1. Serum erythropoietin (mU/ml)

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Baseline</th>
<th>Phase 1 (placebo)</th>
<th>Phase 2 (losartan)</th>
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<tbody>
<tr>
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<td>13.9</td>
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<td>2</td>
<td>*</td>
<td>12</td>
<td>9.7</td>
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</tr>
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</tr>
<tr>
<td>14</td>
<td>*</td>
<td></td>
<td>45.9</td>
</tr>
</tbody>
</table>

*indicates that the test was not performed either due to error of omission or patient drop-out.
cross-over design was an attempt at improving the power of the study.

(iii) The measured serum erythropoietin levels showed marked intra and interindividual variation. Coates [14] contends that for normal individuals, usually the serum erythropoietin remains relatively constant even through some diurnal variation may be seen. Anephric subjects, to maintain erythropoiesis, rely on extrarenal erythropoietin formation for which there is no reflex increase in response to anaemia, although blood transfusion results in reduction in erythropoietin production. An appropriate increase in extrarenal erythropoietin production occurs in response to tissue hypoxia. In the absence of acute hypoxia and transfusion requiring events in our subjects for the duration of their enrolment, one would have to attribute the variability of serum erythropoietin to either sampling or measurement errors. Due to limited resources we were not able to test the reproducibility (coefficient of variance) and accuracy of the assay that we used.

Taking into account the weaknesses of our study, we did not demonstrate any effect of the AIIRA losartan, at the smaller dose, on the erythropoietic response of stable haemodialysis subjects to rHuEpo replacement. In retrospect, the smaller dose, on the erythropoietic response of stable haemodialysis patients could have been improved if we had used a higher dose of losartan, had a less stringent exclusion criteria to allow a higher recruitment rate and had tested the reproducibility of our erythropoietin assay.

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Editor’s note
Please see also the Editorial Comment by MacDougall (pp. 1836–1841 in this issue) and Original Article by Ertürk (pp. 1912–1916 in this issue).