Letters

Femoral neck BMD relative to peak bone mass as 100%.

Fig. 2. Femoral neck BMD relative to peak bone mass as 100%.

Lumbar spine BMD of haemodialysed females.

Fig. 3a. Lumbar spine BMD of haemodialysed females.

Fig. 3b. Lumbar spine BMD of haemodialysed males.

calcium, P alkaline phosphatase and intact PTH. The dialysate fluid used for haemodialysis contained 1.7 mmol/l Ca. CaCO₃ was used as phosphate binder.

BMD were significantly lower in both the lumbar spine (minus 21%, Figure 1) and femoral neck (minus 22%, Figure 2) relative to peak bone mass as 100%. Overall the BMD values were slightly lower in female than male patients, but only in the lumbar spine.

A different pattern emerged when patients were categorized according to age (unfortunately no exact information on menopausal status was available).

As shown in Figures 1 and 2, female patients of less than 50 years of age had significantly higher BMD values than females above 50 years of age. Furthermore, BMD in the lumbar spine was inversely related to age in female, but not in male patients (Figure 3 a, b). A similar relationship was also found in the femoral neck.

The results suggest accelerated bone loss in elderly females, possibly as a result of the menopause [2]. The impact of the menopause on renal osteodystrophy, and the potential necessity to administer female hormones to postmenopausal dialysis patients, have not been properly explored, but in view of the above results this issue definitely deserves investigation.

Albert Szent-Györgyi E. Kiss
Medical University, M. Rajtar,
Szeged, S. Sonkodi
Hungary


Do ACE inhibitors influence the dose of human recombinant erythropoietin in dialysis patients?

Sir,

It has been shown in animal experiments [1] and numerous clinical studies [2-7] that angiotensin-converting enzyme (ACE) inhibitors reduce the effect of endogenous erythropoietin (Epo), leading a reduction in haemoglobin and haematocrit.

Therapy with ACE inhibitors causes a decrease in serum Epo both in healthy volunteers and in patients with diabetes mellitus, renal artery disease, chronic nephropathy and polycystic kidney disease [2,3]. There are also reports describing anaemia in patients with renal transplantation receiving ACE inhibitors as antihypertensive medication, independent of the type of immunosuppressive therapy [4,5].

At the same time, this effect is used to treat erythrocytosis after renal transplantation [6,7] which is described in 15–20% of all kidney transplant recipients. Walter [8] reported decreased haemoglobin and haematocrit in dialysis patients receiving captopril in comparison to patients without captopril treatment despite identical doses of human recombinant erythropoietin (rHuEpo).

We investigated in a retrospective study whether a correlation exists between doses and duration of ACE inhibitors as antihypertensive therapy and the rHuEpo dosage in dialysis patients.

Forty dialysis patients received rHuEpo regularly to obtain a target haematocrit of 30–35%. Twenty of them (50%) received an antihypertensive combination therapy containing an ACE inhibitor (captopril 12.5–75 mg/day, enalapril
The patients were followed for 18 months. The cumulative doses of rHuEpo for every 3 months were determined for each patient. All patients intermittently received an intravenous iron substitution. A monthly control of the blood count provided the basis for the adjustment of the rHuEpo dose needed to obtain the target haematocrit.

We started all patients with a rHuEpo dose of 40 U/kg BW twice weekly. The rHuEpo cumulative dose in patients without ACE inhibitor was 1285 ± 287 U/kg/3 months. In patients with an ACE inhibitor after 1 year of ACE inhibitor treatment the cumulative dose of rHuEpo was higher compared to the patients without ACE inhibitor (8041 ± 4722 U/kg versus 5474 ± 2788 U/kg). However, this increase in rHuEpo dose was not significant before 15 months of treatment (12092 ± 7260 U/kg versus 6449 ± 2650 U/kg; P<0.05, Table 1).

After 15 months the rHuEpo dose increased rapidly, in contrast to patients without ACE inhibitor, where no substantial changes occurred.

Figure 1 shows the total amount of rHuEpo over time in both patient groups. Patients with ACE inhibitors needed more than twice the dose of patients without ACE inhibitor treatment. Other causes of this high-dose rHuEpo treatment such as inflammatory process or malignancy have been excluded.

The patient group without ACE inhibitor treatment had a mean (±SD) ferritin serum concentration of 410 ± 260 µg/l at the start and 481 ± 33 µg/l at the end of the study; the corresponding values of transferrin saturation were 27.4 ± 11.3% versus 34.2 ± 15.2%, and iPTH was 15.9 ± 10.9 pmol/l versus 21.1 ± 26.8 pmol/l. The patient group with ACE inhibitor treatment had a mean (±SD) ferritin serum concentration of 411 ± 260 µg/l at the start and 505 ± 293 µg/l at the end of the study; the corresponding values of transferrin saturation were 25.3 ± 10.9% (control values not measured), and the iPTH levels were 22.2 ± 10.0 pmol/l versus 14.2 ± 7.8 pmol/l.

The aluminium serum concentration and the DFO test were in the normal range. No correlation exists between the dosages of rHuEpo and the ACE inhibitor.

The results of this study show that after a treatment period of 15 months patients with an antihypertensive therapy containing an ACE inhibitor needed a significantly greater dose of rHuEpo to obtain satisfactory haematocrit than did patients without an ACE inhibitor. The understanding of the type of interaction between ACE inhibitors and rHuEpo is still poor.

Yacoob et al. [9] showed that treatment with rHuEpo in normotensive dialysis patients is associated with an inhibition of the renin–angiotensin system, which induces the secretion of Epo by activation of angiotensin II. The ACE inhibitors could further suppress the reduced endogenous Epo production in dialysis patients leading to a greater rHuEpo dose being necessary to obtain a reasonable haematocrit level [3].

On the other hand it is known that high doses of rHuEpo can lead to hypertension. A treatment of this type of hypertension with ACE inhibitors could initiate a circulus vitiosus.

In summary, the findings of this study suggest that in patients with increasing doses of rHuEpo needed to obtain a sufficient haematocrit or with rHuEpo resistance, interactions with other drugs should be considered as causative mechanism. ACE inhibitors seem to play an important role in this regard.

Klinik für Innere Medizin IV
Friedrich-Schiller-University of Jena
H. Sperschneider
Germany


Table 1. Mean values and standard deviation (x ± s) of the cumulative dose of rHuEpo (U/kg BW) 3, 6, 9, 12, 15 and 18 months after beginning of treatment

<table>
<thead>
<tr>
<th>Months</th>
<th>Pat. without ACE inhibitors n = 20 (12 male, 8 female)</th>
<th>Pat. with ACE inhibitors n = 20 (9 male, 11 female)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1680 ± 813</td>
<td>2196 ± 1507</td>
<td>n.s.</td>
</tr>
<tr>
<td>6</td>
<td>3056 ± 1753</td>
<td>3574 ± 2048</td>
<td>n.s.</td>
</tr>
<tr>
<td>9</td>
<td>4528 ± 2232</td>
<td>5441 ± 3057</td>
<td>n.s.</td>
</tr>
<tr>
<td>12</td>
<td>4574 ± 2788</td>
<td>8041 ± 4722</td>
<td>n.s.</td>
</tr>
<tr>
<td>15</td>
<td>6449 ± 2650</td>
<td>12092 ± 7260</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>18</td>
<td>7709 ± 3504</td>
<td>17597 ± 10161</td>
<td>P&lt;0.05</td>
</tr>
</tbody>
</table>

Fig. 1. Total dose of rHuEpo over 18 months in dialysis patients
- • - with (n = 20) and -f- without (n = 20) ACE inhibitors.
Intestinal obstruction complicating calcium polystyrene sulphonate therapy

Sir,

Sodium or calcium polystyrene sulphonate (SPS, CPS) may cause gastrointestinal side-effects such as anorexia, nausea, vomiting and constipation. Large doses in elderly patients may also result in fecal impaction [1,2].

Although these resins are commonly used in uraemic patients, serious adverse abdominal complications are rarely described [3,4]. We report a case of intestinal obstruction requiring surgical treatment in a patient treated with CPS.

A 74-year-old male was hospitalized because of syncope. Medical history included arterial hypertension, a dilated cardiomyopathy and a moderate chronic renal failure. Drug therapy on admission was enalapril, furosemide, spironolactone, digoxin, and warfarin. Physical examination was unremarkable. Blood pressure was 110/70 mmHg and heart rate 98 b.p.m. Laboratory analysis revealed serum sodium 136 mmol/l, potassium 7.7 mmol/l, chloride 112 mmol/l, creatinine 255 μmol/l, and urea 25 mmol/l. Venous blood pH was 7.10 and plasma concentration of bicarbonate 10.4 mmol/l. Urinalysis was normal. An X-ray film of the chest revealed slight cardiac enlargement. A 24-h ECG recording showed an atrial fibrillation with a ventricular rate of 100 per minute.

A presumptive diagnosis of type IV renal tubular acidosis was established. Spironolactone and enalapril were discontinued and insulin, glucose, and bicarbonate were administered. Serum potassium decreased to 6.5 mmol/l and oral CPS, 15 g thrice daily, was prescribed. Because of oral intolerance, the resin was given rectally as a retention enema at a dose of 50 g every 12 h. This treatment was maintained for 8 days because of persistent hyperkalaemia. Constipation appeared on the 4th day of treatment and lactulose was prescribed as laxative. Diffuse abdominal pain, failure to pass gas via the rectum, and abdominal distention appeared 2 days after resin therapy had been stopped. Digital rectal examination revealed an anal fissure and fecal impaction. An abdominal X-ray showed marked colonic distention with fecal material loaded in the descending colon.

Non-operative decompression, including a digital mechanical disimpaction, was unsuccessful. Finally, operative decompression by cecostomy was performed with removal of inspissated faeces including resins. The patient did well after surgery and was discharged. A subsequent colonoscopy revealed no alteration in the colon.

Colonic disease in patients with uraemia is not uncommon. Colonic obstruction, pseudo-obstruction and perforation of the bowel are increased in these patients [5]. Chronic constipation, commonly observed in uraemic patients and worsened by the use of phosphate binders is probably the major predisposing factor to these complications [5]. Phosphate binders cause constipation and may lead to the formation of fecalomas and eventual obstruction. Polystyrene resins may also be associated with altered colonic motility and abnormal bowel function [1,2].

Despite the extended use of these resins only minor adverse gastrointestinal effects have been observed, constipation being the most common. A mild laxative such as sorbitol has been recommended to prevent or treat constipation. Nevertheless, intestinal necrosis associated with the post-operative use of SPS has been reported in uraemic patients when sorbitol is used as its vehicle for oral or rectal administration [6].

In the literature there are only two reports of intestinal obstruction due to CPS therapy [3,4]. In fact this unwanted effect is not included in product information enclosed with the drug. Minford et al. [4] described a 62-year-old male with intestinal obstruction and colonic perforation complicating oral CPS therapy. The resin was initially administered at a dosage of 30 g thrice daily and subsequently at 15 g thrice daily. Duration of treatment was not specified. Concomitant therapy included codydramol, a drug which is also associated with constipation. Despite surgical treatment a fatal outcome ensued.

Foresti [3] reported a case of intestinal obstruction which occurred in an old patient treated with SPS, aluminium hydroxide, and morphine sulphate. Resins were administered at dosage of 15 g daily by oral route during 6 days. The intestinal obstruction was resolved with medical treatment.

Our patient developed intestinal obstruction following CPS therapy. Initial constipation could have been aggravated by the presence of the anal fissure. No other drugs with constipating action were concurrently administered, and the dose of resin prescribed was within the normal range recommended in the literature [1,2]. It is possible that the duration of resin therapy could have been excessive in this case, but no limit is actually defined. We suggest that CPS therapy may itself induce intestinal obstruction in elderly uraemic patients. It may be advisable to limit the duration of therapy in these patients.

Department of Internal Medicine and Nephrology Service, Hospital Universitari Joan XXIII, Spain

G. García-Pardo, A. Martínez-Vea

T. Augusti University Rovira i Virgili, Tarragona, Spain

J. A. Oliver, C. Richart


