

## Research letters

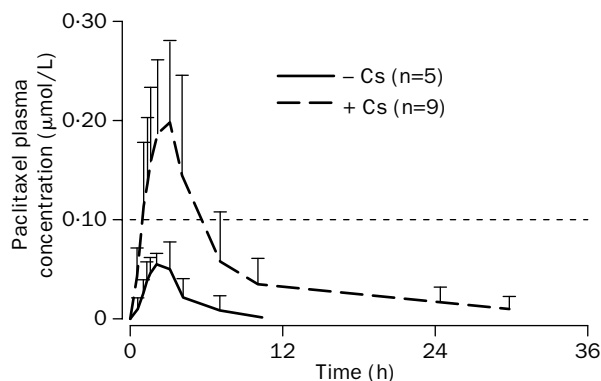
## Co-administration of cyclosporin enables oral therapy with paclitaxel

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Intravenous paclitaxel is associated with unpredictable side-effects largely due to the vehicle, Cremophor EL. Oral paclitaxel, however, is poorly bioavailable due to its high affinity for the multidrug transporter P-glycoprotein (P-gp), abundantly present in the gastrointestinal tract.<sup>1,2</sup> Studies in *mdr1a* (-/-) knockout mice lacking P-gp revealed an increased oral uptake of paclitaxel.<sup>3</sup> We combined oral paclitaxel with the P-gp blocker SDZ PSC 833 or cyclosporin (Cs) in wild-type mice, resulting in a 10-fold increased systemic exposure to paclitaxel.<sup>4</sup> To find out if co-administration of Cs might increase the absorption of oral paclitaxel, a proof-of-concept study was carried out in 14 patients with solid tumours. Five patients received oral paclitaxel (intravenous formulation) at a dose of 60 mg/m<sup>2</sup> during the first course and intravenous paclitaxel at a dose of 175 mg/m<sup>2</sup> during subsequent courses. Nine patients received one course of 60 mg/m<sup>2</sup> oral paclitaxel with 15 mg/kg Cs, and 175 mg/m<sup>2</sup> intravenous paclitaxel subsequently. The first two courses were randomised in these patients and the pharmacokinetics of paclitaxel, Cs, Cremophor EL, and ethanol were determined.

Absorption of oral paclitaxel in combination with Cs was nine-fold higher than after oral paclitaxel alone (figure). After oral paclitaxel with Cs, therapeutic plasma concentrations of paclitaxel above 0.1 µmol were achieved, on average, for 4 h, comparable to an equivalent intravenous dose.<sup>5</sup> After oral paclitaxel alone, plasma concentrations were below the therapeutic range. Apart from a bitter taste, the oral combination was well tolerated. No side-effects associated with Cs administration were observed. The highest detected plasma ethanol concentration was 0.1% (v/v) and Cremophor EL in plasma was undetectable (<0.005% v/v). Maximum Cs concentrations ranged from 2.1 to 4.7 mg/L.

These results show that co-administration of the P-gp inhibitor Cs increases the absorption of oral paclitaxel to therapeutic plasma concentrations. As the safety of the combination at a dose of 60 mg/m<sup>2</sup> paclitaxel is good, oral doses of paclitaxel can be increased or given twice a day. The next goal is to test whether oral paclitaxel is as active as intravenous paclitaxel. The concept of P-gp modulation may well be applied to other drugs with poor bioavailability and high affinity for P-gp such as HIV-1 protease inhibitors.



Plasma concentration time curves of oral paclitaxel with or without Cs represented (mean SD)

The horizontal line indicates a threshold concentration of 0.1 µmol/L; paclitaxel concentrations above are active.

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## Anaemia after enalapril in a child with nephrotic syndrome

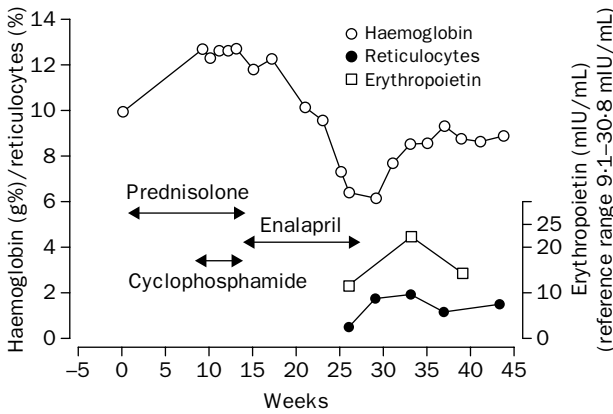
A H Sackey

A girl aged 7 years with focal segmental glomerulosclerosis and nephrotic syndrome failed to respond to prednisolone for 7 weeks, and to prednisolone with cyclophosphamide for a further 8 weeks. Blood pressure was normal and oedema was controlled with diuretics. Creatinine had increased from 30 µmol/L to 50 µmol/L, and the urine protein/creatinine ratio from 2400 mg/mmol to 4000 mg/mmol. From week 10 to week 40, creatinine rose from 30 µmol/L to 85 µmol/L and the urine albumin/creatinine ratio fluctuated between 2000 mg/mmol and 4000 mg/mmol. She was started on enalapril 2.5 mg twice daily. After 3 months, enalapril was discontinued because her haemoglobin had fallen from 127 g/L to 62 g/L with haematocrit of 0.16, but with normal ferritin, folate, and vitamin B<sub>12</sub>. There is a relation between onset of anaemia and use of enalapril (figure). A weaker relation was seen with prednisolone withdrawal.

The association between enalapril use, anaemia, and erythropoietin concentrations has been described in several papers.<sup>1-4</sup> Significant lowering of erythropoietin concentration was shown in a single-blind crossover study of enalapril and captopril in ten healthy volunteers aged between 19 years and 48 years.<sup>5</sup> Gossman et al<sup>3</sup> postulated that angiotensin-converting-enzyme inhibitors decrease erythropoietin concentration by interaction with the renin-angiotensin system, and that in patients with impaired renal function, the lowered erythropoietin concentration may lead to anaemia. The findings in this patient seem to support this hypothesis. The incomplete resolution of anaemia on enalapril withdrawal suggests that other factors, such as worsening renal function, frequent blood sampling, and discontinuation of prednisolone, may have contributed to the initial anaemia.

The manufacturer's data sheet<sup>4</sup> states that there are no studies in children, and the Committee for Safety of Medicines has received no reports of enalapril-associated anaemia in children (personal communication).

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**Changes in indices with enalapril**

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**Anaemia in dialysis patients as a side-effect of sartanes**

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Since 1996, we have used sartanes instead of angiotensin-converting-enzyme inhibitors to control blood pressure in haemodialysis patients. The smooth onset of action and lack of anaphylactoid membrane reactions were the main reasons. Because we had seen unexplained decreases of haemoglobin and delayed r-Hu Epo responses at the start of haemodialysis in some patients on losartan, we were interested in the case-report of Horn and colleagues.<sup>1</sup>

We investigated the data of 184 dialysis patients retrospectively and found that losartan (50 mg/day) had substantially affected haemoglobin concentrations. Of 24 haemodialysis patients on losartan, 18 had decreases in haemoglobin. 14 of these were on r-Hu Epo therapy and had no iron deficiency. Mean haemoglobin concentrations had fallen from 118 g/L to 101 g/L, 4-6 weeks after start of losartan and returned to 112 g/L only after a three-fold to four-fold rise in r-Hu Epo doses.

Since no connection between losartan and anaemia has been made at that time, the drug was withdrawn in only one patient because of hypotension after 6 months. Withdrawal resulted in a rise of haemoglobin from 90 g/L to 135 g/L. Losartan was prescribed several times after withdrawal by her

general physician without our knowledge, and caused similar anaemic episodes each time (figure).

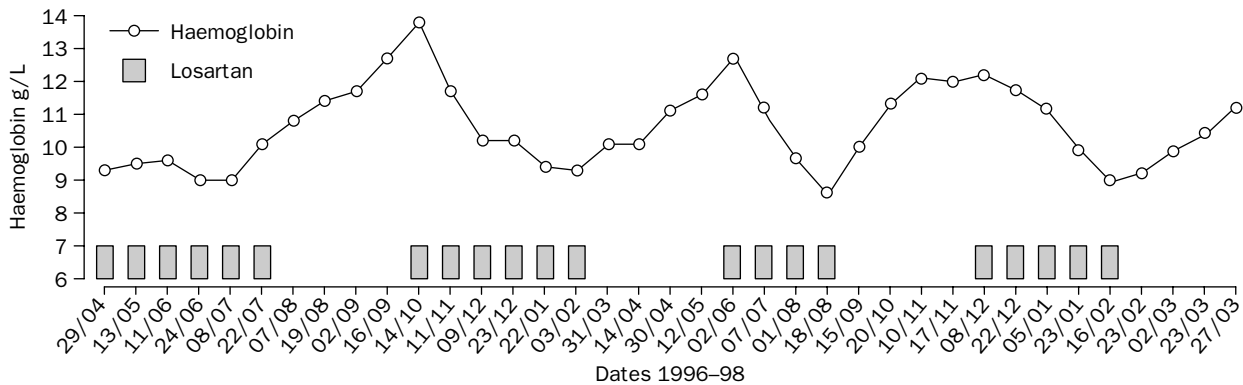
Haematocrit, haemoglobin, and iron stores are closely monitored in dialysis patients, especially when they are on r-Hu Epo therapy. Unexplained decreases led to investigation of overt or hidden blood losses, inadequacy of dialysis doses, or concealed drug abuse. We analysed the data of all our patients treated with sartanes and found that during the past 2 years, 99 patients had been treated with either losartan (96 patients) or irbesartan (3 patients) for hypertension. 26 were on haemodialysis, and 73 had renal insufficiency or renal transplants. Of 12 transplant patients on losartan, two had moderate anaemia, and 12 patients had creatinine clearances to less than 25 mL/min (ten on losartan, two on irbesartan). Marked anaemia was seen only in one severely iron-deficient patient on irbesartan (creatinine 66.3 µmol/L).

Anaemia in patients after transplantation caused by angiotensin-receptor I blockade has been reported,<sup>1,3,4</sup> although the mechanism of action is not clearly understood.<sup>4</sup> Anaemic reactions to sartanes in patients on haemodialysis or predialysis renal insufficiency have been unknown so far. Slight decreases in haemoglobin (0.11 g/dL) are mentioned in the USA but not in Germany.

We wondered whether anaemia has been overlooked during registration trials,<sup>2</sup> contacted the manufacturer of losartan and learned that patients with creatinine of more than 212 µmol/L had been excluded from most studies. According to Toto and colleagues,<sup>5</sup> losartan 50-100 mg/day has been well tolerated by 112 patients with renal insufficiency or on haemodialysis. Retrospectively, there may have been some anaemic reactions were masked through raised r-Hu Epo doses, as in our patients. Stimulation of AT I receptors of erythroid progenitor cells by AT II is believed to increase red-cell mass independently from circulating erythropoietin.<sup>3</sup> If this explanation is true, we do not understand how blockade of the receptor could be surmounted by increasing r-Hu Epo doses. We believe that therapy with sartanes in patients with severe renal insufficiency, haemodialysis, or renal transplants may cause anaemia and, recommend close monitoring of either haemoglobin or haematocrit.

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 4 Brantley RR, Mrug M, Barker CV, et al. Blockade of AT1 receptors lowers hematocrit in post-transplant erythrocytosis. *J Am Soc Nephrol* 1996; **7**: 1939.  
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**Haemoglobin in a patient on losartan**