Pancytopenia due to Paludrine® (Proguanil Hydrochloride)

M.H.M.G.		Houben
S.J.		Hoorntje

Department of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands

M.H.M.G. Houben, MD, Department of Internal Medicine, Catharina Hospital, Michelangelolaan 2, NL-5602 ZA Eindhoven (The Netherlands)

Dear Sir,

We wish to report on severe pancytopenia in a renal transplant recipient with chronic renal failure that occurred after administration of Paludrine® (proguanil hydrochloride; in the following referred to as proguanil) as a prophylactic antimalarial drug and to present hitherto unpublished dosage recommendations for proguanil in patients with renal impairment.

A 25-year-old man went to India in July 1993 for a fortnight holiday. He received proguanil as antimalarial prophylaxis at a daily dosage of 200 mg. His original renal diagnosis was endocapillary proliferative glomerulonephritis; this disease recurred in both renal transplants (1985 and 1992). One week before departure, the serum creatinine concentration was 398 $\mu\text{mol/l}$ (creatinine clearance 10 ml/min). His additional medication included furosemide, felodipine, alu-col, disodium pamidronate, calcitriol, pred-nisone, and immuran (100 mg daily). Spon-

Table 1. Recommended dosage of proguanil in patients with renal impairment

Proguanil dosage

Creatinine clearance ml/min 1.73 m^2

200 mg once daily 100 mg once daily 50 mg every 2nd day 50 mg once weekly

> 60 20-60 10-20

< 10

taneous haemorrhages and epistaxis developed 2 weeks after receiving proguanil. Upon admission to our hospital he appeared pale, cushingoid, and dehydrated. Laboratory findings included anaemia (haemoglobin 5.0 mmol/l), leucopenia (leucocytes 2.7/ nl) with granulopenia (1.28/ nl), and thrombopenia (17/ nl). The serum creatinine level had increased to 641 $\mu\text{mol/l}$. It was concluded that the pancytopenia was caused by a proguanil intoxication. Proguanil and immuran were withheld; additional treatment included thrombocyte concentrates, rehydration, and folic acid. Renal replacement therapy had to be restarted. Both thrombopenia and leucopenia disappeared after 10 days. He eventually made a full recovery though maintenance therapy had to be continued.

Proguanil is generally considered a safe and effective antimalarial drug with few reported side effects [1]. To our knowledge, only two reports of three similar cases with renal impairment and pancytopenia caused by proguanil have been published [2,3]. Proguanil and its active metabolite cycloguanil, a potent inhibitor of dihydrofolate reductase, are predominantly excreted by the kidneys [4, 5]. Therefore, accumulation of the drug is to be anticipated in patients with renal failure, and the dosage has to be adapted in patients with

renal impairment. In table 1 a hitherto unpublished dose regimen is presented for proguanil in patients with renal impairment. This regimen is based on a human dose finding study, initiated by Zeneca Pharma. This study indicated that the maximum plasma concentration, the area under the curve, and the half-lives of proguanil and its metabolites all increased as the renal function decreased. The presented dose regimen should keep the steady state blood cycloguanil concentrations between 15 and 270 µg/l. This is higher than the minimum effective concentration and below toxic concentrations. Haemodialysis and in-traperitoneal dialysis had little effect on the pharmacokinetics of proguanil and its metabolites.

Today's rapidly expanding international travelling with inherent malaria prophylaxis will not exclude renal patients. Nephrologists should be aware of the potential risks and adapt the dosage of proguanil accordingly in patients with renal impairment.

References

Peto TEA, Gilks CF: Strategies for the prevention of malaria in travellers: Comparison of drug regimens by means of risk-benefit analysis. *Lancet* 1986;i:1256-1260. Boots M, Phillips M, Curtis JR: Megaloblastic anemia and pancytopenia due to proguanil in patients with chronic renal failure. *Clin Nephrol* 1982;18:106-108. Tattersall JE, Greenwood RN, Baker LRI, Cat-tel WR: Proguanil poisoning in a hemodialysis patient. *Clin Nephrol* 1987;28:104. Bygbjerg I, Ravn P, Rønn A, Flachs H, Hvid-berg EF: Human pharmacokinetics of proguanil and its metabolites. *Trop Med Parasitol* 1987;38:77-80. Edstein MD, Veenendaal JR, Scott HV, Rieckmann KH: Steady-state kinetics of proguanil and its active metabolite, cycloguanil, in man. *Chemotherapy* 1988;34:385-392.