Dear Sir,

Erythropoietin (EPO) is produced by peritubular cells of the kidney in response to renal hypoxia [1]. In vitro, EPO production may be increased in a dose-dependent manner by atrial natriuretic factor (ANF), an effect mediated by increased cyclic guanosine monophosphate (GMP), the intracellular second messenger of ANF [2]. Inappropriately low EPO production is the major cause of renal anaemia in patients with chronic renal failure (CRF) and therefore agents which increase endogenous EPO production may be of clinical interest.

Inhibitors of ANF metabolism by the enzyme neutral endopeptidase (EC.24.11) have recently become available [3]. We have previously shown that when administered acutely to patients with CRF, these agents produce a prolonged rise in plasma ANF concentration associated with a natriuresis greater than that seen in normal subjects [4] which suggests they may have a potential therapeutic role.

We therefore examined the effect of prolonged plasma ANF elevation through acute neutral endopeptidase inhibition on serum EPO levels in patients with normal glomerular filtration rate, or with moderate or severe CRF. Three groups, each consisting of 8 male patients, were studied: group 1 (normals), GFR 106 ± 8 ml/min/1.73 m² (mean ± SEM); group 2 (moderate CRF), GFR 64 ± 6 ml/min/1.73 m²; group 3 (severe CRF), GFR 16 ± 3 ml/min/1.73 m². Each patient received either the neutral endopeptidase inhibitor, candesartan (Pfizer UK Ltd.) 100 mg intravenously or vehicle (saline) in a double-blind, randomised, crossover study. Plasma ANF (IRMA), urinary cyclic GMP excretion (RIA) and serum EPO (RIA) were measured at baseline, 3 h (peak ANF) and 7 h after administration. The results for the three groups are shown in table 1. ‘Peak’ and 7-hour post-dose results were compared with baseline using paired t tests if prior two-way analysis of variance achieved significance.

Plasma ANF and urinary cyclic GMP excretion rose 2 to 3-fold from baseline in all three groups and remained elevated for at least 7 h in patients with CRF. Despite this, no significant change occurred in serum EPO concentration. No change occurred in any variable in response to vehicle administration. A rise in serum EPO concentration is usually seen within 1-2 h after the onset of stimuli which increase EPO production by the kidney [1].
These results suggest that the stimulatory effects of ANF on EPO production reported with pharmacological concentrations of ANF in vitro are unlikely to be of clinical significance.

Table 1. Plasma ANF, urinary cyclic GMP excretion and serum EPO concentration before, 3 and 7 h after candoxatrilat administration

References