be related to VFA and there was a very good correlation between blood lipids (HDL and triglyceride) and VFA.

In the same issue of the journal, London et al. showed that arterial intimal calcification (AIC) was much more correlated with classical atherosclerosis risk factors in comparison with patients with arterial media calcification (AMC). Whilst, CIMT, PS and SP were highest in the AIC group, age, duration of dialysis and lipids were the independent factors for AIC [2]. Therefore, as shown in this study of Yamauchi et al., in addition to these independent parameters (BMI, SFA and VFA), blood lipids and age should have been included in the multivariate model because of their possible effect on carotid atherosclerosis. Without including them in the analysis, it cannot be concluded reliably whether VFA have any independent significant impact on carotid atherosclerosis.

In a previous study, we showed the significant correlations between CIMT and age, left ventricular mass index, blood pressure and the ACE D allele. In multiple regression analysis, the risk factors for increased CIMT in haemodialysis patients were pre-dialysis systolic blood pressure and the ACE D allele. In the study of Yamauchi et al., whilst no significant difference in the three groups (according to VF) was noticed, there was a tendency that the high VF group was the oldest group. Since age is a well known risk factor for atherosclerosis, it would be interesting to see whether there was any correlation between systemic atherosclerosis measures (CIMT, SP and PS) and age in this study.

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Regression of uraemic pruritus by cyclosporin treatment in a haemodialysis patient

Sir,

Recent studies suggest that low dose (2.5–3.0 mg/kg daily) cyclosporin treatment is an effective, safe and well-tolerated treatment for atopic dermatitis which is refractory to conventional treatment modalities. This treatment can also lead to long-term remission of the disease in some patients [1].

Uraemic pruritus is a distressing disease that is difficult to treat. Its prevalence is high in the dialysis population. An effective treatment of severe uraemic pruritus is needed, as its consequences can be devastating for the patients. We describe the case of a 78-year-old woman who, at the end of 1999, 2 years after the beginning of haemodialysis, developed intense and generalized pruritus. Secondary hyperparathyroidism, dry skin, hyperphosphataemia, anaemia, peripheral neuropathy, high aluminium levels and hypervitaminosis A were all excluded. Although Kt/V was already satisfactory at 1.5, duration of dialysis was increased to 240 min, a more biocompatible membrane (polymethylmethacrylate) was used and swine heparin was changed with an EDTA-purified preparation. Other causes of pruritus (metabolic and endocrine diseases, biliary obstruction, myeloproliferative diseases, polycythaemia vera, iron deficient anaemia and cancer) were excluded.

Symptomatic treatment with antihistamines, steroids and ultraviolet B (UVB) light were ineffective. Rather, the intensity of pruritus worsened, determining a deterioration of the quality of life to the point of an attempted suicide. Therefore, in November 2000, immunosuppressive treatment with cyclosporin was attempted. Starting doses of 200 mg/day were tapered to reach and maintain a therapeutic range between 130 and 160 ng/ml. Serum levels of the drug were monitored weekly at the beginning of treatment and every other week in the maintenance phase. By December 2000, symptoms improved and eventually regressed. In March 2001, cyclosporin was reduced and stopped, but severe pruritus quickly recurred. The patient again expressed suicidal thoughts. Therefore, at the beginning of 2002, a new course of cyclosporin treatment was started. Again, symptoms markedly improved, but in April 2002 treatment was stopped because of cholestatic jaundice due to two biliary stones in the choledocus. Interestingly, jaundice developed in the absence of pruritus, which recurred immediately after the interruption of cyclosporin treatment. Endoscopic papillotomy resolved this complication and in June 2002 treatment with cyclosporin (associated with ursodesoxsolic acid, 300 mg/day) was resumed. Since then, our patient has remained in good clinical and psychological conditions. Cyclosporin demonstrated a good safety profile during long-term treatment and was, generally, tolerated well.

Several different therapies have been proposed for uraemic pruritus: antihistamines, opiate antagonists and even placebo have been reported to be effective in previous reports, but many patients, including ours, do not respond to any treatment. Recently, Mettang et al. [2] pointed out that research on the pathogenesis of uraemic pruritus is concentrating in two areas: the ‘opioid hypothesis’ and the ‘immuno-hypothesis’. The former is controversial and is based on the finding that several μ-receptor-agonistic drugs can induce pruritus and is supported by the observation that administration of opiate antagonists was successful in the treatment of cholestatic pruritus. Indeed, in a preliminary study of uraemic patients, Peer et al. [3] demonstrated that naltrexone, an oral μ-receptor antagonist, was effective in relieving symptoms in all of the treated patients. However, Pauli-Magnus et al. [4] could not reproduce these results in a larger cohort treated for a longer time (4 weeks).

The immuno-hypothesis is the base of the therapeutic approach we chose for our patient. According to this hypothesis, uraemic pruritus is a systemic disease due to a derangement of the immune system with a pro-inflammatory pattern [2]. In support of this hypothesis, uraemic pruritus is extremely rare in transplanted patients with renal failure, as long as cyclosporin treatment is maintained [2]. The IL-2-suppressing effect of cyclosporin might correct the immunological disturbances causing some of the most severe forms of
uraemic pruritus. Our case confirms the efficacy of this approach in a haemodialysis patient with very severe clinical manifestations of the disease, which led her to attempt suicide. In this unblinded single patient we cannot exclude a placebo effect, which can be particularly relevant in patients with pruritus. However, no placebo effect could be observed with all the other treatments (antihistamines, steroids and UVB light) carried out in this patient. In addition, a consistent pharmacological effect from cyclosporin is indicated by the response to challenge, withdrawal and rechallenge.

Although the potential side effects of an immunosuppressive drug in dialysis patients should be kept in mind, our results indicate that cyclosporin treatment might be a new effective approach to severe uraemic pruritus refractory to conventional treatment modalities, provided that appropriate patients are selected and careful monitoring is performed. Our observation and hypothesis need to be confirmed by a placebo-controlled double-blind trial.

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Treatment of digoxin intoxication model by hybrid-kidney with hollowfibre module for clinical haemodialysis

Sir,

Although haemoperfusion is frequently used for the treatment of drug intoxication, this has some disadvantages and its use is limited [1]. We have previously reported a unique hybrid-type artificial kidney by culturing the immortalized renal proximal tubule cells with the introduction of multidrug resistance protein (MDR)-1 in the hollowfibre module for cell culture [2]. Moreover, we scaled up the system by connecting 10 modules in parallel and successfully treated dogs with digoxin intoxication, a substrate of MDR-1 [3]. Although this device was effective for the dog, we should further increase the number of modules connected for future clinical use. Here, we succeeded in scaling up the ‘hybrid-kidney’ by utilizing a single clinically used haemodialyzer and evaluated the efficacy for drug removal in vitro and in dogs with digoxin intoxication.

We used the same cell line, into which cDNA of human MDR-1 [4] was introduced. This clone, named PCTL-MDR, possesses about 100 times larger $K_m$ and $V_{max}$ values for digoxin than control cells, named PCTL [2]. A hollowfibre module available for clinical haemodialysis (APS-08S; Asahi Medical, Tokyo, Japan) made of polysulfone with a surface area of 0.8 m² was purchased. We inoculated the cells onto the hollowfibre by an almost identical method to that reported previously [2,3]. Thus, $5.4 \times 10^9$ cells were injected on the pericapillary side of the module and cultured for 1 week in a CO₂ incubator at 37°C. After incubation, transport of digoxin and inulin from the capillary to pericapillary side were evaluated in vitro. We found that >85% of perfused digoxin was transported from the capillary to pericapillary side by the system with PCTL-MDR, while such transport was only ~10% with PCTL and 20% without cells, respectively. Inulin concentration was not reduced on the venous side by the system with the cells, indicating that leakage did not occur. Next, we applied this to the dog model with digoxin intoxication [3,5]. Using PCTL-MDR, the digoxin concentration decreased to the therapeutic level at the end of a 3-h treatment. Although treatment with PCTL reduced digoxin concentration, the observed decrease was significantly smaller than with PCTL-MDR (Figure 1).

Estimated digoxin clearance with PCTL-MDR was 31±2 ml/min. Slight leukocytopenia and thrombocytopenia, and elevated activity of circulating granulocyte elastase, was detected. However, the magnitude of these parameters was similar between three trials, and dogs tolerated this treatment well. Comparing digoxin clearance in the present experiments with that of adult [6], we propose to treat patients by increasing surface area of the single haemodialyzer to 2 m², which is now commercially available. Thus, the present results suggest that our scaled-up module has sufficient capacity to treat digoxin-intoxicated patients, especially when complicated by renal failure. It might be useful to apply it to various types of artificial hybrid-kidneys with different types of cells for the treatment of patients in the future.

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