long-term use of these compounds are lacking, however, and animal studies examining the impact of very long-term administration have not been performed. Documented adverse effects in humans induced by high-dose administration over months or years include the milk-alkali syndrome [2] and hypophosphataemic osteomalacia [3]. Our patient admitted to consuming Bisodol®, an OTC preparation which contains calcium carbonate 522 mg, light magnesium carbonate 68 mg and sodium bicarbonate 64 mg in each tablet. Given his dosing history, one can conservatively estimate a cumulative intake of 57–114 kg calcium carbonate, 7.5–15 kg of magnesium carbonate, and 7–14 kg of sodium bicarbonate over more than 3 decades. In contrast to the milk-alkali syndrome, which characteristically presents with the triad of metabolic alkalosis, hypercalcaemia and nephrocalcinosis [4], our patient presented with haematuria and renal failure although it should be noted that the serum bicarbonate and calcium were disproportionately preserved in contrast to the degree of renal failure, suggesting the Bisodol® was ameliorating the metabolic effects of advanced renal failure.

Long-term urinary alkalinization has not previously been documented as causing either interstitial nephritis or transitional-cell cancer. Our hypothesis is based clinically on the similarities between this case and the analgesic syndrome [6], a detailed history of OTC medication ingestion is indi-cated that they would treat hypertriglyceridaemia; some used a variable dyslipidaemia.


Treatment of dyslipidaemia in renal disease

Sir,

We were interested to read the article by Pedro-Bolet et al. [1] calling for specific guidelines for the treatment of dyslipidaemia in renal failure. The data they present on the incidence of lipid abnormalities and the potential pitfalls of estimating LDL-cholesterol from the Friedewald formula in haemodialysis patients do not provide any answers to the important question they pose in the title of their paper i.e. when to treat dyslipidaemia in patients with chronic renal failure on haemodialysis? The absence of controlled studies of lipid lowering strategies in renal failure patients makes it impossible to produce truly evidence-based guidelines on this topic. Clinicians, therefore, have to decide whether it is possible to extrapolate from the increasing evidence in the general population that cholesterol-lowering therapy reduces myocardial events in middle-aged men [2,3] to a heterogeneous population with a high incidence of vascular disease but a variable dyslipidaemia.

The lack of consensus on this subject in the UK is illustrated by a survey one of us (GW) carried out in 1993–1994 of the treatment of lipid abnormalities in renal disease in UK. A questionnaire was sent to 191 consultant nephrologists enquiring about the treatment of lipid abnormalities by diet and/or drugs in patients with nephrotic syndrome or treated by haemodialysis, continuous ambulatory peritoneal dialysis, or renal transplantation. The response rate was 45%. Of these, the majority treated hypercholesterolaemia in patients with nephrotic syndrome (80%) and in renal transplant recipients (81%). Approximately two-thirds of clinicians would use hypolipidaemic drugs in these conditions either as first line or after a trial of diet. A lower percentage of patients on CAPD (68%) or haemodialysis (66%) were deemed to merit treatment and only 50% of respondents would use hypolipidaemic drugs in dialysis patients. Most clinicians used total cholesterol to guide decisions to treat but perhaps most strikingly the ‘action value’ at which drug therapy would be instituted varied widely from 5.5–12.0 mmol/l. Nearly 50% of clinicians indicated that they would treat hypertriglyceridaemia; some used LDL- or HDL-cholesterol to help guide drug therapy. HMG CoA reductase inhibitors were first line drugs for 80% of clinicians in nephrotic syndrome and dialysis patients. Fibric acid derivatives were more commonly used in the transplant recipients (29%).

These data are somewhat difficult to interpret since decisions to treat hyperlipidaemia would involve an overall assessment of coronary risk and this was impossible to assess by questionnaire. However, these data probably overestimate the degree of intervention since it is likely that non-respondents would be less likely to treat hyperlipidaemia.
Recently we have introduced guidelines to target patients with end-stage renal failure and hypercholesterolaemia who might be considered to be at increased cardiovascular risk according to the recommendations of the British Hyperlipidaemia Association [4]. We have identified a number of patients with known coronary artery disease with significant, untreated hypercholesterolaemia. They have subsequently had substantial reductions in total serum cholesterol concentrations with HMG CoA reductase inhibitors without adverse events. We believe that the current evidence [2,3] is now too strong to withhold hypolipidaemic drug therapy in this specific subgroup which, however, only accounts for a small percentage of end stage renal failure patients (only 6% of patients in the paper by Pedro-Botet had LDL-cholesterol > 3.4 mmol/l). Nephrologists would not hesitate to treat hypertension in ESRF despite the lack of controlled studies of treatment in these patients. The question of treatment of other dyslipidaemias in renal disease (e.g. hypertriglyceridaemia, low HDL-cholesterol, apolipoprotein abnormalities) does require further study and will only be resolved by prospective, controlled, randomized studies. Although the logistical problems are formidable, the high cardiovascular event rate in the ESRF population should prompt definitive studies to be performed and there is a pressing need to define strategies to decrease the high mortality in ESRF patients. This will require cooperation between nephrology departments perhaps organised by national or international organisations such as the European Renal Association. While such studies are awaited, we would suggest that it is important to identify and treat those patients with renal disease at high cardiovascular risk based on known modifiable risk factors including total and LDL-cholesterol concentrations.

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Reply by authors

Sir,

We agree with Dr Warwick's comments concerning treatment of dyslipidaemia in renal disease. Uraemic dyslipidaemia is characterized by a complex disturbance of plasma lipid metabolism resulting in significant changes in lipoprotein composition. Thus, simple measurement of plasma lipids tends to underestimate the severity of the metabolic derangement. On the other hand, independently of the precision and accuracy of low density lipoprotein (LDL) determination, LDL cholesterol tends to be in or below the desirable range. Dyslipidaemia of patients with chronic renal failure, including normolipemics, is mainly characterised by abnormalities in triglyceride-rich lipoproteins with the presence of atherogenic species of very low density lipoproteins and accumulation of remnants in serum, together with increased levels of lipoprotein(a) and low high density lipoproteins (HDL).

Furthermore, since the Second Report of the National Cholesterol Education Program [1] does not recommend treatment in healthy subjects with high triglycerides and low HDL cholesterol, it is very unrealistic to recommend initiation of treatment even in patients with secondary dyslipidaemia. We consider that specific guidelines for treatment of dyslipidaemia in patients with renal disease should be defined by an expert committee on the basis of data, and data for modifying current recommendations are not yet available.

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Plasma thrombomodulin concentrations in uraemic children

Sir,

There are deleterious effects of end-stage renal disease (ESRD) on endothelial cells leading to coagulation abnormalities. Furthermore, bioincompatibility of the haemodialysis (HD) material together with HD-associated vascular changes contribute to a prothrombotic state and possibly accelerated atherosclerosis [1].

Thrombomodulin is located on the endothelial surfaces and released by endothelial injury and/or stimulation. It is a key protein for the activation of protein C, which in turn inactivates activated factors V and VIII, and accelerates fibrinolysis. Therefore thrombomodulin plays a crucial role in the regulation of blood coagulation and fibrinolysis. Furthermore, increased plasma thrombomodulin has been accepted as a sensible marker for endothelial vascular damage and atherosclerosis [2].

Tissue-type plasminogen activator (t-PA) activates the fibrinolytic system and is inhibited by fast-acting plasminogen activator inhibitors (PAI) [3].

The aim of this study was to evaluate the role of uraemia on the release of endothelial-derived haemostatic factors, namely thrombomodulin and t-PA, in paediatric ESRD patients undergoing regular HD.

Thirteen uraemic children (7 boys, 6 girls), aged between 8 and 18 years (mean age 14.8 years), undergoing haemodialysis on hollow-fibre dialysers with cuprophane membranes 3 days weekly for 4.1 years, were enrolled in the study. Underlying diseases were chronic glomerulonephritis in seven cases, reflux nephropathy in five cases, and juvenile nephrophthisis in one case. All but one were hypertensive and had been stable on the same antihypertensive drug therapy for at least 8 weeks during the study protocol. Ten cases had