dialysis patients, effective disposal of dietary K load has to rely mostly, if not entirely, on the dialysis procedure itself. In fact, the paper by Hussain *et al*. [1], and few previous observations [4], indicate that extrarenal K disposal in dialysis patients may be quantitatively relevant enough to result in dangerous hyperkalaemia when aldosterone effects are pharmacologically inhibited, unless parallel changes on dialysate K concentration are also made.

We have been able to asses the relevance of extrarenal aldosterone effects on the control of plasma K levels in dialysis patients in a patient with Addison's disease. This patient, a 73-year-old female with autosomal dominant polycystic kidney disease, had been on dialysis for 3 years. She also had a polyglandular autoimmune hypofunction syndrome, resulting in hypoparathyroidism, hypothyroidism, recurrent pericarditis and global adrenal insufficiency. The latter diagnosis had been made 25 years ago and was supported by very low urine 17-keto and 17-hydroxycorticosteroids unresponsive to exogenous ACTH and increased levels of plasma ACTH, renin and K levels. She was treated with thyroxin, glucocorticoid and mineralocorticoid (fludrocortisone 0.1 mg/day) oral substitution. Her pre-dialysis plasma K usually ranged from 4.5 to 5.7 mmol/l. She was dialysed three times weekly for 4.5 h, by use of a 1.6 m^2 polyamide-membrane filter and a custom bicarbonate dialysate with 2 mmol/l K concentration. Her interdialytic weight gain was constant at <2.5 kg and Kt/V values ranged from 1.19 to 1.35. Since fludrocortisone is not available in Italy, and its use was considered non-essential in the context of chronic dialysis treatment, it was stopped in February 2002 (dialysis schedule and all other medications remaining unchanged). Glucocorticoid therapy consisted of methylprednisolone 8 mg in the morning and 2 mg in the evening (this over-substitutive dosage was accounted for by a pericarditis episode 2 months earlier). Last pre-dialysis plasma K was 5.5. Two weeks after fludrocortisone was withdrawn, plasma K was 6.3, the patient began complaining of progressive lassitude and numbness and after an additional 10 days pre-dialysis plasma K was 7.8 mmol/l. No other possible causes of hyperkalaemia could be found and, specifically, intestinal bleeding, fistula malfunction and dietary K load were all excluded. Fludrocortisone (0.1 mg/day) was restarted, with a progressive fall in plasma K levels. Since then, her pre-dialysis K levels have been stable at 4.8–5.3 mmol/l. Urine excretion was 300–500 ml/day, with a K content (on fludrocortisone therapy) of <3 mmol/day, indicating that renal contribution to overall K balance was negligible and that fludrocortisone was likely to affect K excretion through the colon. Even though transcellular K shift cannot be ruled out in an acute setting [6], this mechanism cannot account for chronic changes in plasma K levels, which instead require changes in K balance. In dialysis patients, on a fixed dialysis schedule, balance changes may occur only at the intestinal level.

This observation teaches us that also in anuric patients aldosterone is not a useless hormone and that mineralocorticoid function has to be substituted in the occasional patient with adrenal failure and on regular dialysis treatment. Enhanced extrarenal effects of aldosterone on K balance in uraemia may limit the safety of antialdosterone drugs in patients on chronic dialysis treatment.

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Drug interaction between sevelamer and cyclosporin

Sir,

We read with interest the original report made by Miguel-Angel Guillen-Anaya and Michel Jadoul [1] of a drug interaction between sevelamer and cyclosporin (CsA) occurring in a liver transplant patient treated also by chronic haemodialysis. After sevelamer was started, the CsA trough levels reached values as low as 35 ng/ml and they dropped again after rechallenge. As potential explanation, the authors suggest that CsA absorption, which is bile-dependent [2], could be hampered by the fact that sevelamer binds bile acids in the gastrointestinal (GI) tract. Interestingly, in the clinical study performed by Jensen *et al*. [3], the bile acid sequestrant cholestyramine (4 g given at noon) did not interfere with CsA absorption.

We would like to mention that sevelamer is a poly(allylaminehydrochloride) polymer that may bind not only phosphate and bile acids, as the authors point out, but also cholesterol, vitamins D, E and K and folic acid [4]. A direct binding of a lipophilic substance such as CsA – and by extension also tacrolimus – appears, therefore, as an additional and more likely explanation.

This observation points to the distinction to be made between the two types of phosphate binding in the GI tract: (i) a specific one achieved by aluminium hydroxide and calcium salts and (ii) a non-specific binding attained by polymers such as sevelamer. This absence of specificity might be of less importance for vitamins or folic acid absorption, but may put the patient at risk when lipophilic agents such as immunosuppressive and/or other drugs (lipophilic statins?) are prescribed. Under those circumstances, it appears that sevelamer should be used with caution, i.e. at sufficient time lag to potentially interfering drugs and only when specific (and less expensive) phosphate binders are contraindicated.

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Comment on letter by Deray

Sir,
In his letter, Deray has attempted to identify a single, fixed dose conversion ratio when switching patients from epoetin to darbepoetin alfa therapy and has concluded that this ratio is not the same for the intravenous (i.v.) and subcutaneous (s.c.) routes of administration [1].

In trying to identify single, fixed dose conversion ratios by the s.c. and i.v. routes, Deray has compared the results from a European study in epoetin-naïve pre-dialysis patients [2] with a US study in haemodialysis patients receiving prior stable epoetin therapy [3]. As neither of these studies was designed to investigate conversion methodologies and as they involve different patient populations and routes of administration, it is misleading to draw conclusions from them about conversion ratios.

Furthermore, as has been pointed out previously [4,5], the implementation of a single, fixed dose ratio to convert patients from epoetin to darbepoetin alfa is not appropriate for either the i.v. or s.c. routes of administration, as the relationship between epoetin and darbepoetin alfa doses is non-linear. As well as being influenced by prior epoetin dose, the conversion ratio will also be influenced by other factors such as dosing interval. This is why the European prescribing information for darbepoetin alfa suggests 200:1 as an initial conversion ratio (based on equivalent peptide mass) but notes that 'titration to optimal therapeutic doses is expected for individual patients'. In the two studies cited by Deray, 42 [2] and 69% [3] of patients required further dose titration after starting darbepoetin alfa. In the first study, the patients had been naïve to all epoetin-related therapies, prior to starting darbepoetin alfa. In the second study, patients were switched from epoetin to darbepoetin alfa therapy.

It is therefore incorrect to speculate, on the basis of single conversion ratios calculated from mean data from dissimilar studies, that switching from SC epoetin to darbepoetin alfa would necessitate a dose increase of 20–30%. As I stated in my original article [6], formal head-to-head studies are required before any definite conclusions can be made about the relative cost–benefit of these two therapies.

Lastly, Deray cites an abstract by Hörl [7] to support his contention that switching from darbepoetin alfa once every 2 weeks to a 3-week dosing schedule necessitates a 13% increase in dose. However, this abstract does not make any mention about 3-week dosing, so it is difficult to understand how he reached this conclusion. Studies in dialysis patients have shown that there is no dose penalty associated with changing from darbepoetin alfa dosing once every 2 weeks to once every 3 weeks [8] and, likewise, only a 0–2.2% increase in total weekly dose was necessary when changing to dosing once every 4 weeks [8,9]. Again, more controlled studies are required to examine the true cost-effectiveness of darbepoetin alfa dosing less frequently than once per week.

I completely agree with Deray in that attempts to reduce the total cost of anaemia therapy are of the utmost importance to allow more patients to benefit. Pending further studies, and for this reason, treatment should be individualized to each patient's particular requirements, rather than by indiscriminately applying arbitrary dosing algorithms.

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Myalgia: an uncommon or underestimated side effect of mycophenolate mophetil after transplantation?

Sir,
Mycophenolate mophetil (MMF) is widely used after transplantation and in several autoimmune disorders.