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Reply

Sir,

We thank Dr Sakkas and colleagues for their interest in our recent article demonstrating the impact of nocturnal home haemodialysis on exercise capacity and duration [1]. We agree with Sakkas et al. that exercise intolerance as exhibited by patients with end-stage renal disease (ESRD) is likely to be multifactorial [2,3].

Excessive daytime sleep and sleep disorders, including sleep apnoea syndrome, occur with increased frequency in patients with ESRD [4]. Although the exact contribution of sleep disorders, particularly sleep apnoea syndrome, on physical intolerance is unknown in ESRD, as similar observations were made with patients with heart failure and central sleep apnoea treated with continuous positive airway pressure [5].

To date, there is an emerging body of literature indicating the effect of intensive haemodialysis on various surrogate outcomes. The ultimate impact of nocturnal haemodialysis on the mortality of ESRD patients remained to be clarified.

Conflict of interest statement. None declared.

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Acute kidney injury due to deferoxamine in a renal transplant patient

Sir,

We have served as members of the Renal Safety Board for deferasirox (Exjade®, ICL670) for the past 5 years and wish to respond to a misleading comment on the renal safety profile of deferasirox that appears in the discussion section of a recent article by Clajus et al. [1], which describes a case report of acute kidney injury due to deferoxamine. The authors state that deferasirox has ‘been repeatedly shown to cause acute renal failure’, citing a recent article by Kontogiorghes [2].

It should be pointed out that Kontogiorghes bases many of his conclusions about the tolerability of deferasirox on post-marketing surveillance information. Such events are reported in the drug label irrespective of whether a causal link has been established. More than 30 000 patients have been treated with deferasirox outside the clinical trial setting, many of whom were elderly or had other underlying medical conditions in addition to transfusional iron overload. Although acute renal failure was reported in a very small number of patients receiving deferasirox, almost all of these patients had severe complications of their underlying haematological disease, most commonly sepsis, and the contribution of deferasirox to the renal insufficiency in these critically ill patients is quite uncertain. Having reviewed many of these cases in detail, we are very skeptical that deferasirox was responsible for the episodes of renal failure. In addition, the term ‘acute renal failure’ was probably used inappropriately in many cases to describe relatively minor increases in serum creatinine (<2 × upper limit of normal) that developed over the course of several weeks.

Conflict of interest statement. C.P. is a consultant of Novartis, Italy, for transplantation and autoimmune diseases.

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Reply

Sir,

We would like to thank Dr Hirschberg and colleagues for their interest in our report, which was aimed to raise awareness of the rare but repeatedly described untoward effects of deferoxamine on renal function. Moreover, we aimed to propose a mechanism by which these untoward effects on renal function could be mediated [2]. In the discussion we stated that a different drug, deferasirox, has ‘been repeatedly shown to cause acute renal failure’ quoting a recent paper by Kontoghiorghes [3]. Dr Hirschberg and colleagues, who, as members of the renal safety board for deferasirox, had detailed knowledge of the post-marketing surveillance data, are ‘very sceptical’ that deferasirox was responsible for these cases of acute renal failure.

We can only refer to data available in the public domain. According to the FDA website, there had been 115 reports of suspected adverse drug reactions in the association with the use of deferasirox from 2 November 2005 to 20 June 2006 (http://www.fda.gov/cder/dsn/2007_fall/nme.htm). Sixteen unduplicated reports described renal adverse events. Seven patients improved after discontinuation of deferasirox. Seven patients had ‘acute renal failure’ with an onset between 5 and 58 days after initiation of the therapy. Dr Hirschberg and colleagues state that ‘the term acute renal failure was inappropriately used in many cases to describe a relatively minor increase in serum creatinine (<2× upper limit of normal) that developed over the course of several weeks’. Unfortunately, there had been no uniformly accepted definition of acute renal failure [4]. However, in a variety of settings, there is accumulating evidence that small increments in serum creatinine are associated with adverse outcomes [4]. Therefore, the term acute kidney injury (increase of creatinine >25 µmol/l over 48 h), which is often superimposed on pre-existing CKD, was recently introduced. This definition will increase the clinical awareness and the detection of injury to the kidney and should, in our view, also be used in the setting of pharmacovigilance. Aside from the FDA information, Vichinsky et al. [5] showed in 132 adult and paediatric patients that deferasirox administration was accompanied in a mild and stable increase of serum creatinine in 36.4% of the patients. Of the 63 patients in that study that received deferoxamine, 22.2% experienced such an increase of serum creatinine. In contrast to deferoxamine, where the mean change in creatinine was 3.06 µmol/l, the mean increase in the deferasirox-treated group was 6.3 µmol/l. Unfortunately, serum creatinine only rises after a substantial loss of glomerular filtration rate and is also influenced by many factors like gender, weight and race. Estimation of glomerular filtration rate, e.g. by measuring cystatin C, would therefore be the preferred way to monitor renal function. Data on proteinuria, another important marker of renal damage, are missing completely.

As vividly illustrated by the post-marketing information of Novartis on deferasirox (14 May 2007), a pro-active approach to potential, even rare side effects of new drugs are in the best interest of the public. A uniform assessment of renal function and renal injury, e.g. by determination of estimated GFR and proteinuria, as proposed in a science advisory of the AHA for the assessment of patients with or at increased risk for cardiovascular disease [1], would provide a better scientific basis for the monitoring of untoward renal effects of new drugs.

Conflict of interest statement: Investigator initiated trials by Dr J. T. Kielstein supported by Novartis, Europe.

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1. Brosius FCr, Hostetter TH, Kelepouris E et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. Circulation 2006; 114: 1083–1087

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HDF promise for the future

Sir,

The February issue of Nephrology Dialysis Transplantation amply reported on online haemodiafiltration (HDF) as a possible promise for the future [1].

Please note the following erratum in Table 1 of the Editorial Comment, concerning our study with reference 16: high-volume HDF in postdilution was compared with