changing the administration route. Scan J Urol Nephrol 1995; 29: 11–14

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Reply

Sir,

I would like to thank Lars Weiss for his interesting comments regarding my Editorial Comment [1] from over a year ago! However, I do have some difficulty accepting one or two of his arguments. While one cannot completely exclude the possibility of different pharmacodynamics between epoetin alfa and epoetin beta, I feel it is unlikely that a difference in intravenous (i.v.) half-life of 6.8±2.7 h for i.v. epoetin alfa and 8.8±2.2 h for i.v. epoetin beta, along with 19.4±10.7 h for subcutaneous (s.c.) epoetin alfa and 24.2±11.2 h for s.c. epoetin beta [2] can really make a substantial difference to biological activity. There may be other differences between epoetin alfa and epoetin beta previously unrecognized, but it would be surprising if such subtle differences in pharmacokinetics in a study conducted in healthy volunteers translated into an enhanced clinical efficacy.

However, I do accept completely Weiss’s comment that inclusion criteria including only iron-replete and well-dialysed patients should be ‘regarded as standard in trials of dialysis patients’. As I said in my Editorial Comment [1], and in a follow-up Reply Letter [3], it is always difficult to extrapolate results from scientific studies into everyday clinical practice. While one cannot criticize the inclusion criteria in either the Swedish [4] or Italian [5] studies, the experience of Jones et al. [6] and Geddes and Woo [7] testify to this. I also disagree with Weiss’s comment that a Kt/V of >1 and a ferritin level of >200 μg/l are the ‘norm’ in dialysis units; I accept the unpublished data from the Swedish Society of Nephrology, but it is well known that Sweden boasts some of the best results in renal anaemia management in Europe (as reported in the ESAM survey [8]), and the experience in other countries in Europe falls far short of the results that Weiss quotes. Thus, I still feel that we should be cautious about extrapolating results from well-controlled clinical trials into everyday clinical practice in our dialysis units.

Finally, although half-lives aren’t everything, before getting too excited about a possible difference between 19.4 and 24.2 h for s.c. administration of epoetin alfa and epoetin beta, respectively, one should not forget that the half-life for s.c. darbepoetin alfa is substantially greater at 48.8±12.7 h [9].

Conflict of interest statement. I have received honoraria, travel grants and research funds from Amgen, Ortho Biotech and Roche Pharmaceuticals.

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The clinical significance of aldosterone in ESRD: Part II

Sir,

We would like to congratulate Epstein for his excellent review of the rapid advances in our understanding of the non-classical effects of aldosterone [1]; however, allow us to add one small word of caution. While the role of aldosterone in endothelial dysfunction is clear and its deleterious effect on survival of patients with cardiovascular disease is undisputed, its clinical significance and effect on survival is not yet demonstrated in patients with end-stage renal disease (ESRD). As recently noted in this Journal, often risk factors for overall and cardiovascular mortality in the general population, such as a high cholesterol [2], obesity [2,3] or hypertension [3,4] are either not found to be risk factors or are paradoxically associated with improved survival. Hyperkalaemia with resulting sustained elevation of aldosterone levels in haemodialysis patients may be an important risk factor in their accelerated atherosclerosis; but perhaps it is not. Over a decade ago, we evaluated the significance of serum aldosterone levels upon non-renal potassium elimination in patients on dialysis. We found a group of patients who were unable to mount an aldosterone response to hyperkalaemia who maintained persistently low levels of aldosterone despite a potassium challenge [5]. Most of the patients in that study are now deceased. When we recently evaluated the data, we found that the effect of the inability to secrete aldosterone appeared not to be protective. Patients with higher aldosterone levels tended to have longer survival (Figure 1). Although we did not find that the aldosterone level was as significant as dietary restriction in potassium homeostasis, it is possible that some of the benefit may have been due to the aldosterone itself. Of course, there were confounding factors. The patients who were unable to mount an aldosterone response to hyperkalaemia were usually those with hyporeninaemic hypoaldosteronism; who, in turn, were more likely
to have ESRD diagnoses of diabetes and sickle cell anaemia. We already knew that patients with those diagnoses do not have prolonged survival on dialysis. Therefore, it does not necessarily mean that high aldosterone levels improve the survival of haemodialysis patients, but may merely mean that those with the diagnoses that are prone to have low levels have poor survival. The effect may be similar to those recently related [3] for the apparently positive effects of obesity and hypertension. It may not be that obesity prolongs the survival of dialysis patients, but merely that patients who are thin from malnutrition merely skew the data to look that way. Like the author of that editorial comment, I would suggest that a reasonable and prudent approach to the subject would be to reserve judgement at present and wait for further studies.

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Reply

Sir,

I am grateful to the authors of the letter for their praise and laudatory comments regarding my comprehensive review on aldosterone and progressive renal disease.

The authors raise two interesting questions, which are worthy of consideration—i.e. (i) the complexity of the determinants of aldosterone secretion and (ii) whether circulating aldosterone levels constitute an appropriate marker for cardiovascular and renal risk. (i) In 1978 we conducted a study assessing the role of volume per se as the determinant of plasma aldosterone in anephric man [1]. The rationale was that this would provide a ‘unique window’ for assessing the effects of volume, independent of the confounding effects of the renin angiotensin system. This study emphasized the critical importance of avoiding changes in volume during the interdialytic intervals in order to assess the role of volume on aldosterone. Implicit in this is the notion that any determinations of aldosterone in ESRD patients without rigorous maintenance of the constancy of volume during the interdialytic period usually confounds the observed results. (ii) Recent additional considerations regarding our unique new understanding of aldosterone indicates that any simplistic correlation of serum aldosterone levels with target organ dysfunction is overly simplistic. In a recent review [2], I have delineated why circulating aldosterone levels fail to predict either CV and renal risk or the therapeutic benefit of aldosterone receptor blockade. In brief, recent studies indicate that synthesis of aldosterone occurs at extra-adrenal sites, including the endothelium and vascular smooth muscle cells (VSMC), showing direct evidence that vascular cells per se are aldosteronogenic. Duprez et al. [3] proposed that locally produced aldosterone in the vascular endothelial cell may act on the VSMC through binding to the receptor, thereby acting in a paracrine manner. Secondly, the ostensible dissociation cited by the authors of the letter is consistent with the formulation that the determinants of aldosterone effects include both ambient aldosterone levels and aldosterone responsiveness per se. Observations by Horiuchi et al. [4] and Takeda et al. [5] are consistent with an increase in aldosterone responsiveness. Clearly aldosterone response can be readily dissociated from circulating aldosterone levels. Consequently, only utilization of aldosterone receptor antagonists as a pharmacological probe can rigorously unmask the pathogenetic role of aldosterone.

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