Cinacalcet and vascular calcifications induced by calcitriol

Sir,

We read with great interest the article by Henley et al. [1] showing that cinacalcet could not prevent vascular calcifications induced by calcitriol in uraemic rats and would like to make the following comments:

(1) This inefficiency might be explained by the stability of the calcium \times phosphate (Ca \times PO_4) product because the decrease in serum calcium (SCa) was compensated by an increase in SPO_4. Indeed at the end of the study, the mean SPO_4 of the three measurements (before and 4-24 hours after the dose) was 1.4 mg/dl (29%) higher when cinacalcet was compared with vehicle and 1.9 mg/dl (23%) higher when cinacalcet + calcitriol was compared with calcitriol alone.

(2) This hyperphosphataemic effect of cinacalcet in uraemic rats has already been reported with the first generation calcimimetic NPS558 [2] and is in complete agreement with the mirror image of the trade off theory of secondary hyperparathyroidism in uraemia developed by Slatopolsky and Bricker [3]: hyperparathyroidism is the price the organism pays to eliminate phosphate retention induced by the reduction of its glomerular filtration.

(3) These experimental results do not contradict the decrease in SPO_4 reported in dialysis patients receiving cinacalcet [4]. This decrease was, however, mild (7%) when 1zOH vitamin D was stable and almost twice smaller when 1zOH vitamin D was increased [5]. This difference can probably be explained by the fact that when vitamin D is increased to correct cinacalcet-induced hypocalcaemia, PO_4 absorption is increased, whereas when CaCO_3 is used instead, this latter complexes phosphate in the gut and decreases SPO_4.

(4) These deleterious effects of calcitriol in uraemic rats and patients contrast with beneficial effects of an increased oral calcium-load:

- In uraemic rats, high calcium diet alone has been shown to decrease mortality in association with a lower SPO_4 and a decrease in proteinuria and blood pressure associated with a lower expression of the AT1-receptor of angiotensin II [6]. In uraemic mice with ApoE gene deletion-induced atherosclerosis, high calcium is also quite effective in decreasing aortic calcifications [7].

- In dialysis patients, never exposed to aluminium, high CaCO_3 dose (6–9 g per day taken as phosphate binder) at 2.4–3.6 g of elemental calcium, without 1zOH vitamin D, but with calcidiol repletion, a dialysate calcium concentration of 1.5 mmol/l (not inducing negative per-dialytic calcium balance), a good control of hyperparathyroidism can be obtained (usual PTH <220 pg/ml in two third of the patients) without hypercalcaemia nor hyperphosphoraemia. This results in a good preservation of bone mineral density (BMD), especially of the cortical bone, without any inverse correlation between BMD and vascular calcification, as has been reported in dialysis patients using 1zOH-vitamin D [8]. The only independent risk factors for vascular calcifications were age and duration on dialysis, whereas phosphocalcic, plasmatic and therapeutic parameters were in no way correlated [9].

(5) Therefore we think that these experimental and clinical data should lead to revision of certain therapeutic recommendations made by the NKF K/DOQI in 2003 before cinacalcet was on the market [10].

- To definitely limit the use of 1zOH vitamin D in uraemic patients and to rely mainly on calcidiol repletion (>30 ng/ml) to take advantage of the multiple health benefits given by the sunshine vitamin [11]. This approach should be recommended, not only for the CKD grade 3-4 patients (as is already done by NKF/K/DOQI of 2003), but also for dialysis patients.

- To use 1zOH vitamin D only with non-calcic-phosphate binders in order to prevent a SPO_4 increase above 1.50 mmol/l in predialysis patients and >1.60 mmol/l in the dialysis patients.

- To give priority to Ca oral phosphate binders over 1zOH vitamin D to correct the cinacalcet-induced hypocalcaemia both in dialysis and predialysis patients.

- To use cinacalcet in predialysis patients (repleted in calcitriol) to control their hyperparathyroidism only when their SPO_4 is controlled by Ca-phosphate binder, and their SCa is increasing above 2.37 mmol/l, the upper limit of the optimal range suggested by the last USRD study, since it pointed to a significant increase in mortality risk above this threshold [4].

Conflict of interest statement. None declared.

The association between BP and mortality in patients on chronic peritoneal dialysis

Sir,

We read with interest the article from Goldfarb-Rumyantzev et al. on the association between a single blood pressure (BP) recording approximately 2 months after the start of chronic peritoneal dialysis (PD) and subsequent mortality during a mean follow-up of 25 ± 14 months [1]. The authors showed that low systolic BP (<111 mmHg) was associated with a higher mortality rate, whereas high systolic BP (up to 220 mmHg) was not associated with an increased mortality risk. Based on these associations, the authors conclude that ‘aggressive treatment of hypertension in the PD population should be cautioned’. In our opinion, this study does not provide the evidence for this conclusion. Although Goldfarb-Rumyantzev et al. present interesting associations, they do not show that treatment of hypertension, either by optimization of the hydration status or by the use of anti-hypertensive drugs is harmful with regard to outcome. Therefore, in our opinion the results of this observational study should primarily be used to generate hypotheses that must first be investigated in properly designed studies before we change our attitude towards hypertension in PD patients.

The association between systolic BP <110 mmHg and increased mortality was found only in certain subgroups: in patients with diabetes, in patients with a history of heart failure, and in patients treated with antihypertensive medications (in 51, 32 and 81% of the study population, respectively). Since the proportion of diabetics in incident dialysis patients is much lower in most European countries in comparison with the USA (e.g. 17% in the Netherlands in 2002), the results of this study may not fully apply to the present European situation. It follows that there probably is no association between low systolic BP and increased mortality in the vast majority of European PD patients.

With regard to the use of antihypertensive medications, the authors suggest that systolic BP <110 mmHg resulted from ‘overaggressive treatment of hypertension’. We think that there is a more likely explanation. It is conceivable that patients with severe heart failure (and systolic BP <110 mmHg) were treated with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and/or beta-blockers for the indication of heart failure and not because of hypertension. Unfortunately, the authors did not provide information on the classes of antihypertensive drugs that were used nor on the indications for the use of these drugs.

Systolic BP <110 mmHg at 2 months after the start of PD was present in only 57 (5.4%) of the total study population of 1053 patients. It would be interesting to characterize this subgroup in more detail with regard to co-morbidity, nutritional status, smoking status, medication use and the course of blood pressure over time. Notably, the authors did not include smoking status as a covariate in their model. Smoking may be a stronger risk factor and compete with hypertension in causing mortality [2].

By stating that ‘high BP does not have any negative implications for survival’ the authors imply that high BP in PD patients may be favourable with regard to outcome. In this study, however, it is difficult to interpret the exact nature of the association between high BP and outcome. The authors used a single BP recording at approximately 2 months after the start of PD and we are not informed on the course of BP during follow-up. One of the most prevalent causes of hypertension in PD patients is fluid overload. We are not informed on the hydration status of the study population. An additional argument to be cautious with hypertension is that Goldfarb-Rumyantzev et al. demonstrated that diastolic BP >110 mmHg tended to be associated with a higher mortality rate (P = 0.09). Finally, the use of anti-hypertensive drugs may confer an independent protective effect on mortality in dialysis patients [2,3]. Previously, the survival advantage of high blood pressure was only found in haemodialysis patients who were taking anti-hypertensive medication [4]. Likewise, it is possible that hypertension did increase mortality in the study of Goldfarb-Rumyantzev et al., while the negative impact on survival was balanced by a protective effect of antihypertensive medication.

In conclusion, this study again shows that the relationship between BP and outcome in dialysis patients is extremely complex. At present, the optimal BP goal in PD (and haemodialysis) patients is unknown [2]. In our opinion, this issue can only be solved by prospective randomized studies on the effect of both pharmacological and non-pharmacological (e.g. optimization of fluid status) treatment of hypertension in well-defined groups of dialysis patients.

Conflict of interest statement. None declared.

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