Secondary Hyperparathyroidism, Anemia and Treatment with 1.25(OH)₂D₃ in Uremia

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Dear Sir,

We read with interest the report by Docci et al. [1] in this journal on the role of secondary hyperparathyroidism in the genesis of the hemolytic component of the anemia in uremia. The study allows the conclusion that the osmotic fragility of red blood cells in uremic and dialysis patients is increased but there is a lack of correlation between this abnormality and secondary hyperparathyroidism. To confirm this data they claim that treatment with 1.25(OH)₂D₃ was effective in controlling blood levels of parathyroid hormone (PTH) but unable to normalize the osmotic fragility of red blood cells in their patients. In a recent paper Docci et al. [2] report a similar failure to ameliorate the platelet function by the treatment with 1.25(OH)₂D₃ in uremics on conservative therapy. Massry and Akmal [3] criticize Docci et al., among other things, by the fact that their data show '... blood levels of PTH almost 14 times the normal value after treatment with this vitamine D metabolite...'.

We observe that Docci et al. [1, 2] measured immuno-reactive parathyroid hormone (iPTH) with an antiserum which detects both the intact hormone and the C-terminal fragment and, as they say, there are probably unknown amounts of inactive or active fragments of circulating PTH in the blood of their patients. As reviewed by Massry [4], only the intact PTH and the N¹⁻³⁴-terminal fragment but not the C-terminal fragment may have a negative effect on erythropoiesis or survival of red blood cells. Many studies [5-7] have demonstrated that therapy with 1.25(OH)₂D₃ lowers iPTH in uremic patients; however, only a C-terminal iPTH assay has been used.

To specify the effect of 6 months of therapy with 1.25(OH)₂D₃ (0.25-0.5 µg daily) on secondary hyperparathyroidism, we have evaluated, before and after the treatment, the blood levels of iPTH in a group of 15 uremic patients on maintenance hemodialysis, not only with C-terminal iPTH assay but also with midregion iPTH assay.

The midregion iPTH assay, as shown by Roos et al. [8], specifically reflects the parathyroid secretory activity by the antiserum for 34-64 PTH fragment. In fact midregion iPTH, but not C-terminal iPTH, clearly increases during EDTA hypocalcemia and in all hyperparathyroid sera. Moreover, this fragment is not rapidly metabolized like intact PTH or the N¹⁻³⁴-terminal fragment of PTH.

Our uremic patients had various forms of secondary hyperparathyroidism (tertiary hyperparathyroidism was excluded by bone biopsy) and discontinued therapy with vitamin D metabolites 2 months before starting with the 1.25(OH)₂D₃ treatment. During the therapy, in all patients, we evaluated serum ionized calcium (Ca⁺⁺) levels between 1.30 and 1.35 mmol/l (normal values, at pH 7.40, 1.15–1.30 mmol/l).

The results of our preliminary study (fig. 1) confirm that short treatment with 1.25(OH)₂D₃ may significantly lower blood levels of C-terminal iPTH but that it is unable to demonstrate a significant effect on circulating midregion iPTH.

In conclusion, we bring further evidence for the difficulty of the biochemical evaluation of secondary hyperparathyroidism in renal failure and that uremic patients, despite 6 months of efficacious treatment with 1.25(OH)₂D₃, may have high circulating levels of toxic iPTH fragments and/or an exaggerated acute parathyroid secretory activity. We would like to specify that short treatment with 1.25(OH)₂D₃ may be an ineffectual test to evaluate the influence of the PTH moiety and the secondary hyperparathyroidism on anemia of uremic patients. On the other hand, a rise in hemoglobin in patients with hyperparathyroidism is reported, in significant studies, only after parathyroidectomy [4].

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$I = 1$ $p < 0.01$ 1
 $M \pm SD 4.7 \pm 2.5$ $M \pm SD 1.7 \pm 1$

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BEFORE treatm. AFTER treatm.

p NS

$M \pm SD 8.5 \pm 6.5$ $M \pm SD 7.1 \pm 6$

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BEFORE treatm.

AFTER treatm.

Fig. 1. Effects of treatment with 1.25(OH)₂D₃ for 6 months (0.25–0.5 µg daily) on serum C-terminal iPTH (PTH-C) and midregion iPTH (PTH-M) in 15 uremic patients on maintenance hemodi-alysis. Mean values ± SD before and after treatment analysed by Student t-test.