LETTER TO THE EDITOR

Is long-term bisphosphonate administration associated with significantly increased circulating parathormone levels in patients with multiple myeloma?

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Multiple myeloma (MM), a malignant disorder of mature B cells, is associated with osteolytic bone disease (MM-BD), resulting not only from disease deposition but also the production of soluble factors that increase bone resorption through osteoclastic activity (1). Pharmacological intervention as supportive care in these patients has resulted in specific reduction in MM-BD-associated morbidity (2). Bisphosphonates are stable analogues of naturally occurring pyrophosphates that absorb onto bone surfaces and inhibit bone resorption (3). Initially used to treat malignancy-associated hypercalcaemia, they have been proven to significantly reduce myeloma-associated skeletal morbidity, gaining widespread acceptance over the past 10 years (2).

The skeletal half-life of bisphosphonates is long (1,2); however, the accumulation of these compounds does not appear to result in cumulative effects on bone metabolism (4). Whilst the long-term (>2 years) effect of pamidronate or zolendronate in patients with breast cancer and MM was not associated with any electrolyte or haematological imbalance compared with baseline measurements (5), the effect on the parathyroid activity has not been studied in detail. The present study was conducted to examine the effect of long-term bisphosphonate therapy on the plasma parathormone (PTH) and vitamin D metabolite (1,25 Vit D3) activity in patients with MM, relating the analysis to duration of exposure and the presence of concomitant renal dysfunction.

Twenty-two patients with MM (de novo, n = 7; plateau phase/off therapy, n = 12; refractory disease, n = 3) with a median age of 67 years (range 37–91 years) received intravenous infusions of pamidronate (90 mg of pamidronate sodium; Aredia, Novartis Pharmaceutical) every 4 weeks for a median of 18 months (range 5–48). Electrolyte analysis was performed, according to the institutional laboratory Standard Operating Procedures, before treatment as a baseline and at the time of the study. At a single, given time point, the electrolyte and PTH measurements were performed in triplicate and the data was expressed as a mean±standard error of the mean (S.E.M.).

Patients were examined for the presence of abnormal renal function (ARF) (serum creatinine > upper limit of normal, on three serial estimations; ARF: 297±88 μmol/l cf. normal renal function (NRF): 74±4 μmol/l, P = 0.03). In all patients evaluated, no significant changes from baseline electrolyte measurements were demonstrable with no alteration in the serum adjusted Ca2+ (2.33±0.02 mmol/l; normal range (NR): 2.15–2.55), phosphate (1.21±0.06 mmol/l: NR: 0.8–1.5), magnesium (0.81±0.02 mmol/l: NR: 0.7–1.05) or alkaline phosphatase (224±28 IU/l; NR: 98–450). Twenty-four per cent of patients’ serum Ca2+ concentration were detected in the lower quartile of the normal range with more patients within the ARF group demonstrating lower Ca2+ than the NRF group (44% cf. 12.5%) though no overall significant difference was noted (2.32±0.05 mmol/l cf. 2.33±0.02 mmol/l, P = 0.4). No significant difference in serum phosphate (P = 0.4), magnesium (P = 0.34) or alkaline phosphatase (P = 0.2) was demonstrated between the ARF and NRF groups, confirming the results previously reported (5).

The mean plasma PTH level in the study group (n = 22) was measured at 19.6±5.8 pmol/l (NR: 1.3–7.6) and the mean plasma level of the vitamin D metabolite, 1,25 Vit D3, was recorded within the normal range at 61.0±14.9 nmol/l (NR: 20–120). No significant difference in the plasma level of 1,25 Vit D3 (35.3±17.6 pmol/l cf. 72.5±19.8 pmol/l, P = 0.08) or PTH (28.1±16.1 nmol/l cf. 16.1±6.1 nmol/l, P = 0.22) was demonstrable in the presence or absence of renal dysfunction (Fig. 1A). The long-term administration of bisphosphonate therapy was not associated with any measurable alteration in the renal phosphate clearance (with a phosphate/creatinine ratio: 0.138±0.022; phosphate excretion index: −0.026±0.036; % tubular phosphate resorption: 86.2%±2.2).

This is the first evidence of an association between increased PTH activity and long-term pamidronate administration in patients with MM. Secondary hyperparathyroidism is associated with chronic hypocalcaemia, vitamin D deficiency and chronic renal failure resulting from hyperphosphataemia, which was not demonstrated in this study. Furthermore, the elevated PTH levels did not relate to vitamin...
D deficiency as plasma levels of one of its metabolites (1,25 Vit D₃) were unaffected by the prolonged bisphosphonate administration. No evidence of osteitis fibrosa was demonstrated on routine skeletal surveys nor did any patient demonstrate features of tertiary hyperparathyroidism.

Baseline PTH levels prior to the commencement of pamidronate infusions were not available. No correlation between duration of bisphosphonate exposure and plasma PTH levels was demonstrated (regression analysis: \( r^2 = -0.053, P = 0.98, n = 22 \)), irrespective of renal function (ARF: \( r^2 = 0.037, P = 0.49, n = 15 \) cf. NRF: \( r^2 = 0.023, P = 0.77, n = 6 \)).

In light of the elevated PTH levels, a sub-group of patients (\( n = 6 \)) were studied prospectively with measurements of plasma PTH levels pre-therapy and monthly thereafter for 5 months. In this group, the mean plasma PTH level rose above the upper limit normal range after the first infusion of pamidronate and continued to rise steadily, though a wide variation in individual patient PTH levels in this small group meant that the increase in PTH level for the group as a whole did not reach statistical significance at 4 months (\( P = 0.06 \); Fig. 1B). The downward trend observed at the 5-month period after initiation of therapy may be the result of homeostatic mechanisms influencing the plasma level of PTH, which is subsequently surpassed by long-term exposure.

The clinical relevance of these findings remains to be clarified and further study, prospectively, is merited. In particular, it would be worth investigating what effect the newer generation of bisphosphonates, which are more potent, exert on circulating PTH activity and electrolyte homeostasis. The contribution of concomitant therapy, including steroids, to the raised PTH levels cannot be ruled out though the study of patients with MM-BD not receiving bisphosphonate therapy as a control group could be deemed to be unethical in light of published guidelines (6). It is not known if the finding of increased PTH activity is potentially detrimental and, as yet, has no implications on the duration of therapy. However, if such increased PTH activity were to be clinically relevant in patients with MM-BD, specific therapy to reduce the increased PTH activity may alleviate this potential problem.

References

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