We read with great interest the paper by Saad et al. (1), which reported that zoledronic acid effectively reduces metastasis related bone pain and skeletal complications in patients with metastatic prostate cancer. We are particularly interested in the zoledronic acid-induced elevation in serum parathyroid hormone (PTH) levels that was initially reported by Saad et al. (2). Levels of serum parathyroid hormone, increased statistically significantly more in patients who received zoledronic acid at 4 mg (81.8%, 95% CI = 56.3% to 111.1%; \(P = .001\)) or at 8/4 mg (90%, 95% CI = 57.9% to 126.7%; \(P = .001\)) than in patients who received the placebo (17.1%, 95% CI = 3.3% to 27.5). Is elevation of serum PTH secondary to zoledronic acid-induced hypocalcemia? If not, what is the mechanism of such elevation?

We are currently using zoledronic acid in patients with metastatic prostate and breast cancers. We have found that zoledronic acid can induce hypocalcemia even in patients with normal serum levels of calcium, and that serum PTH levels are elevated in such patients. Because the skeleton is a major store of the body’s calcium, osteoclast-mediated bone resorption constitutes an important mechanism that restores normal serum calcium concentrations in patients with hypocalcemia of diverse etiology. Zoledronic acid exerts its effect on the skeleton by inhibiting osteoclast activity in bone and by substantially reducing osteoclastic bone resorption. It also lowers serum calcium levels and was initially approved for the treatment of hypercalcemia associated with malignancy.

Serum calcium concentration is a potent regulator of PTH synthesis, and hypocalcemia is a major stimulator of PTH release. PTH increases serum calcium concentration by activating bone resorption; PTH also increases renal tubular calcium reabsorption and renal calcitriol production. PTH has multiple effects on the bones: it increases the number of bone cells, both osteoblasts and osteoclasts, and stimulates bone remodeling. When given (or secreted) continuously, PTH stimulates osteoclastic bone resorption. However, intermittent administration of PTH in animals or osteoporotic patients also stimulates bone formation (3). In addition, in a worldwide placebo-controlled trial, PTH as monotherapy caused a statistically significant reduction in fracture incidence (4).

Zoledronic acid-induced hypocalcemia usually appears several days after administration of the drug and resolves within 2–3 weeks. Because zoledronic acid is usually given as a once-monthly intravenous regimen, it seems logical to suggest that it could induce an intermittent elevation of serum PTH levels. PTH would then act on osteoblasts via PTH receptors, increasing their activity and leading to a net stimulation of bone formation rather than bone breakdown. We suggest that, in addition to inhibiting osteoclast-mediated bone resorption, zoledronic acid also indirectly stimulates bone formation via its effect on PTH release. This mechanism may constitute an additional positive effect of zoledronic acid therapy on bone metabolism in patients with metastatic tumors.

Saad et al. (2) originally reported that patients who received zoledronic acid had a statistically significant elevation in serum PTH levels compared with those who received placebo. It would be interesting if they were to examine whether further reductions in bone-related complications are associated with serum
PTH levels in the patients with elevated serum PTH levels.

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REFERENCES


NOTES

Editor’s note: Saad et al. declined an invitation to respond to this correspondence.

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