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Newer Therapies in Hypercalcemia and Metabolic Bone Disease

Hunter Heath III, MD*

The decade of the ‘80s has been an exciting one for all investigators in the area of calcium and bone metabolism because a remarkable convergence of technology, basic science applications, and clinical interest has led to major advances in understanding this area. The physiology of calcium-regulating hormone secretion and action, mechanisms of plasma calcium homeostasis, the cellular basis of metabolic bone disease—all have yielded to concerted attack. However, the practicing physician has seen much of this advance somewhat from the sidelines, asking legitimately when this new information was going to be translated into practical measures for care of patients. This session was intended to address this justified query and to point out several important therapeutic maneuvers that are available now, are about to see general use, or represent promising first approaches to new agents. We focused on three important areas: the life-threatening hypercalcemia frequently accompanying malignant tumors, aluminum-related renal osteodystrophy, and osteoporosis.

Hypercalcemia of Malignancy

The pathogenesis of hypercalcemia in malignancy is complex and varies among tumor types. The older classification as “ectopic parathyroid hormone (PTH)-secreting” versus that caused by direct tumor destruction of bone was based on indirect and largely mistaken premises. Secretion of authentic PTH by non-parathyroid tumors has never been convincingly demonstrated, and tumor metastases are now known to destroy bone indirectly, by stimulating generation and activity of osteoclasts. It is now clear that almost all nonparathyroidal malignant tumors causing hypercalcemia do so by secreting or inducing the formation of factors that in turn stimulate osteoclasts. One such tumor product is a 141-amino acid peptide with some PTH-like structure and bioactivities. This PTH-related peptide (PTHrP) lyses bone but also stimulates renal tubular reabsorption of calcium; these two actions may account for the viciousness of the ensuing hypercalcemia. Other direct or indirect tumor hypercalcemic substances may include 1,25-dihydroxyvitamin D, prostaglandins, transforming growth factors, and other peptide cytokines.

Biphosphonate treatment of severe hypercalcemia

Aside from various antitumor measures, there are no effective ways to inhibit secretion of hypercalcemic factors. Thus, treatment of the hypercalcemia has focused first on inhibition of osteoclasts and second on enhancing renal excretion of calcium. Body (1) reviewed agents currently available, then concentrated on the biphosphonates (diphosphonates). These synthetic analogs of pyrophosphate are potent inhibitors of bone resorption but have varying potencies and mechanisms of action. They are effective against the osteolytic component of hypercalcemia, but do not alter renal tubular reabsorption of calcium, and therefore are relatively ineffective when the latter is a major causative factor.

The only biphosphonate currently approved and on sale in the United States is also the least useful in hypercalcemia: etidronate (EHDP) or Didronel®. It is ineffective against hypercalcemia when given orally but is effective intravenously. Several other biphosphonates have had considerable testing in Europe and generally seem to be more effective than etidronate. For example, clodronate (dichloromethylene biphosphonate) at 100 to 300 mg/day for up to ten days can restore normocalcemia in up to 90% of cases. However, relapse may occur rapidly after discontinuance of clodronate. Amidronate (APD) (or AHP BP) is very effective when given as two-hour infusions of 15 mg/day for up to 10 days. Doses less than 0.25 mg/kg/day are ineffective. This drug is efficacious whether or not skeletal metastases are present. Importantly, normocalcemia may last for several weeks after stopping amidronate, and its toxicity is low, including transient fever and lymphopenia.

Still newer biphosphonates of even greater potency than amidronate are being tested abroad, and some of them are being tested in clinical trials in the United States. It seems likely that within a few years we shall have available extremely potent biphosphonates capable of inducing prolonged normocalcemia in cancer patients, and some of these agents may be active orally. It is possible that these agents could also reverse or prevent skeletal destruction by metastases.

Potential use of gallium nitrate and WR-2721 in the treatment of hypercalcemia and hyperparathyroidism

Bonjour et al (2) discussed two antihypercalcemic agents that are much further from general use than the biphosphonates: gallium nitrate, and WR-2721 (an organic thiophosphate). Gallium nitrate has been used for scanning bone and tumors, but because of its localization in nonskeletal malignancies, it saw further development as a chemotherapeutic agent. During initial human studies, investigators occasionally saw transient hypocalcemia, apparently caused by gallium nitrate. In vitro studies indicated a direct effect of the compound on PTH- or lymphokine-stimulated bone resorption, and further clinical in-
vestigations suggested that it might be an effective antihypercalcinic agent in various types of malignancies. A recent, randomized, double-blind study suggested that gallium nitrate is effective in lowering the hypercalcemia of malignancy and that it may be superior to maximally effective doses of calcitonin. The clinical use of gallium nitrate is not yet at hand, because proper comparative studies versus other agents, such as methramycin and the biphosphonates, are not yet available. Further studies are also needed to better understand gallium nitrate's mechanisms of action. The existing data suggest that gallium nitrate or compounds derived therefrom may be very effective in the acute treatment of humoral hypercalcemia of malignancy.

WR-2721 was also developed as a potential cancer therapeutic agent to increase the resistance of normal tissues to ionizing radiation and alkylating chemotherapeutic agents. Just as for gallium nitrate, the hypocalcemic action of WR-2721 was noted incidentally during phase I clinical trials. WR-2721 is a remarkable compound in that it both decreases the secretion of PTH in vitro and in vivo and directly inhibits renal tubular reabsorption of calcium. Furthermore, WR-2721 may directly inhibit osteoclastic bone resorption. Some evidence suggests that WR-2721 is less potent than biphosphonates or gallium nitrate, but more clinical studies are necessary. It is not yet clear whether WR-2721 can inhibit secretion of the PTH-related peptide from tumors, but if it can it would have remarkable triple efficacy in treating the humoral hypercalcemia of malignancy. Just as for gallium nitrate, the very fact that WR-2721 has its known effects greatly encourages the search for related compounds that may be highly effective in treating hypercalcemia of multiple causes.

**Aluminum-Associated Renal Osteodystrophy**

**Therapy of aluminum-related bone disease**

Malluche and Faugere (3) described the syndromes of bone disease related to skeletal aluminum accumulation that can occur in patients undergoing chronic hemodialysis. The aluminum is ingested as aluminum hydroxide-containing phosphate-binding antacid gels or enters from contaminated dialysis solutions. Excess bone aluminum may be demonstrable in nearly half of patients on chronic dialysis and can occur even in mild to moderate renal failure. In particular, stainable aluminum gathers at the interface between unmineralized bone matrix (osteoid) and mineralized bone, and it appears to impair the mineralization process. Clinical manifestations of aluminum-associated bone disease include bone pain, fractures, and hypercalcemia. The latter must be carefully differentiated from the hypercalcemia of "tertiary" hyperparathyroidism, because parathyroidectomy may only aggravate aluminum-associated bone disease.

Malluche and Faugere (3) discussed chelation therapy with the iron-binder, deferoxamine (Desferal®), which also binds aluminum. Deferoxamine binds circulating aluminum ion, which is then removed during dialysis. The lowered plasma aluminum level reverses the blood-bone concentration gradient, and thus allows aluminum to diffuse out of bone. Important reductions in bone aluminum can follow several months of treatment.

The histologic manifestations of aluminum-associated bone disease vary from so-called "aplastic" or adynamic bone (no active bone formation or resorption, and no excess osteoid) to florid osteomalacia. In all cases he has treated, Dr. Malluche thought that aluminum chelation yielded improvement, although reminding us that whatever other type of renal osteodystrophy preceded or accompanied the aluminum accumulation would remain or emerge.

Deferoxamine therapy has serious side effects, potentially including hypotension, angina, and ocular damage. Because of this and the difficulties in selecting cases for chelation therapy, the treatment is best undertaken only after appropriate studies on iliac crest bone biopsies and consultation with a nephrologist experienced in use of the drug. More long-term studies are needed to establish firmly the safety and effectiveness of deferoxamine in renal osteodystrophy.

**Osteoporosis**

Of all problems related to bone and calcium metabolism, the clinical and economic impact of late-life and postmenopausal osteoporosis is the greatest. While acute care of hip fracture alone costs several billion dollars per year in the United States, the worldwide cost in human suffering and national resources is incalculable. While we have made dramatic progress toward understanding the causes of bone loss, physicians have been frustrated by the few treatment options available. In particular, they are impatient with the lack of treatments to increase bone mass, rather than just slow its loss. In this part of the session, we focused on new ways to deliver old treatments (transdermal estrogen) and preliminary reports on efficacy of two methods to increase bone mass (fluoride and PTH).

**New methods of administration of estrogens**

Lindsay (4) outlined trends in estrogen prescription over recent years and highlighted controversies over risks and benefits of estrogen treatment after the menopause. Estrogen clearly retards or even stops bone loss after the menopause but increases bone mass little if at all. Estrogen therapy may also decrease the risk of cardiovascular disease, but on the other hand the risk of endometrial carcinoma is increased. While simultaneous use of a progestin, with endometrial shedding, seems to eliminate that risk, the relative effects on cardiovascular risk and bone mass remain unclear.

Similarly, delivery of estrogen transdermally bypasses the liver and reduces certain estrogen effects mediated by the liver (eg, increased plasma binding proteins and clotting factors). It is not yet known if transdermal estrogen is cardioprotective or if its salutary effect on bone equals that of oral estrogen. Trials in osteoporosis are under way, but it will be a long time before all the answers are in on how best to give estrogen, to whom, and for how long. The transdermal route for estrogen is likely to be available soon as a treatment alternative.

**The role of sodium fluoride in the treatment of osteoporosis**

Current studies with sodium fluoride (NaF) were summarized by Riggs et al (5). It has been known for many years that skeletal
Fluorosis can result in sclerotic bones, but only over the last five years have there been two long-term, placebo-controlled trials of NaF in established osteoporosis, one at the Mayo Clinic, and one at Henry Ford Hospital. The authors described preliminary data from the Mayo study, which is nearing completion. In brief, more than half of the patients taking NaF have had increased lumbar spine bone mineral density, but NaF had no effect at all on appendicular (cortical) bone mass. The drug therefore may be of benefit only to those primarily suffering from the crush fracture syndrome. Furthermore, there was a significant minority who did not respond to NaF, and the treatment was associated with a fairly high incidence of various side effects, including gastric irritation and bleeding, anemia, and lower-extremity pain from stress fractures. Data on fracture rates are still being obtained. Obviously, antifracture efficacy of NaF must be determined before it can be approved for general use. Because the bone generated during NaF treatment is structurally abnormal, it is possible (but unlikely) that the increased bone mass would not stop fracturing. The bone community eagerly awaits definitive reports from both of the large trials to see if NaF will find a major role in treatment of osteoporosis.

**Parathyroid peptide (hPTH 1-34) in the treatment of osteoporosis**

Reeve et al (6) gave an update on clinical trials with a seemingly paradoxical treatment for osteoporosis: parenteral synthetic PTH fragment 1-34 [hPTH-(1-34)]. In hyperparathyroid diseases, endogenous PTH generally causes bone loss, but intermittent elevation of PTH in animals by injection sometimes causes osteosclerosis. Reeve and colleagues have taken advantage of the fact that PTH can increase bone formation as well as resorption. They have administered hPTH-(1-34) as once-daily injections alone or in combination with 1,25-dihydroxyvitamin D or estrogen. The latter compounds were given to enhance calcium absorption, which does not reliably follow intermittent elevations of plasma PTH.

When daily hPTH-(1-34) was given alone, they saw increased trabecular volume in iliac crest biopsies but neutral calcium balance and decreased femoral bone mass. In early studies, alternating hPTH-(1-34) for six weeks with 1,25-dihydroxyvitamin D for six weeks appeared to increase spinal bone mass, as did combination of hPTH-(1-34) with estrogen.

This work is important for what it teaches about physiology of bone, but application of hPTH-(1-34) to clinical practice in these complex regimens is problematic. The peptide is very expensive and must be given parenterally. Further, the difficulty in finding a simple, safe, and effective regimen is somewhat discouraging. At a minimum, this work shows that bone formation can be increased by something other than fluoride and certainly will encourage continued research.

**Final Note**

This session showed that safe, effective acute therapy for life-threatening hypercalcemia is now available and will soon be even better, that alternative methods for administering estrogen will soon be out, and that effective treatments to increase bone mass (at least in the spine) are feasible and may reach clinical use within the next five years. If advances in the coming decade match those of the last, it may not be too much to hope that death and morbidity from several bone and calcium disorders could be virtually eliminated before the end of the century.

**References**