INTRODUCTION

We have investigated a combined PTH-Calcitonin therapy to enhance reduced bone mass in osteoporotic patients. Previous therapy protocols using calcium, vitamin D, estrogen, sodium fluoride, or combinations of these drugs, have not been successful in enhancing bone mass more than 10% in one year especially in low turn-over states. Studies using ana-bolic doses of the PTH fragment 1-34 hPTH have produced modest gains documented by histomorphometry. A recent report of Slovik et al. (1) clearly showed PTH to be effective in enhancing vertebral bone density, measured by quantitated computed tomography (QCT). Rasmussen et al. (2) proposed to additionally reduce bone resorption by combing the phosphate stimulated endogenous PTH secretion with calcitonin injections. This concept was effective in enhancing trabecular bone mass on histomorphometric analysis. Others described the addition of calcitonin to PTH treatment not being effective (3, 1). The objective of our study was to develop a novel approach to combination therapy (see patient and study design). N-terminal PTH and nasally applied calcitonin were used to induce a positive bone balance in osteoporotic patients. Changes in bone density were monitored by quantitative CT-methods (QCT).

PATIENTS AND STUDY DESIGN

Patients: We studies 8 patients (6 male, 2 female) with osteoporosis, documented by bone biopsy of the iliac crest, x-ray and bone density measurements. The females were postmenopausal, but the etiology of the disease in the male subjects was unclear. In one case alcohol abuse may be a causal factor (patient 1). Informed consent was obtained from each patient after ethical committee approval to the study.

Study design: The whole treatment period lasted nearly 14 months including 4 therapeutic cycles of 104 days. 1 cycle consisted of 70 day treatment with PTH (1-38 hPTH s.c. 720-750 U daily) followed by 2 weeks of calcitonin (100 IU nasal spray twice daily) and a 3 week medication free pause. During PTH treatment calcitonin was added for periods of 14 days starting on day 15 and 43 respectively.
Peptides: The 1-38 hPTH peptide was from Bachem, Torrance, California, one ampoule containing 720-750 U compared with the standard NIBSC 82/508 by bioassay monitoring the cAMP production of renal cortical membranes (4). Salmon calcitonin nasal spray was from Sandoz AG, Freiburg, FRG, one bottle providing 100 U/stroke, 40% reaching the circulation.

Bone density: Bone density was determined for cortical bone at the lower forearm by single photon absorbtiometry (SPA) and for trabecular bone of the spine by quantitated computed tomography (QCT) with the single (SEQCT) and dual energy (DEQCT) technique (the latter method was additionally used in pat. 4-8) using the UCSF calibration phantom.

Vertebral height: To exclude further wedging of vertebral bodies we calculated the indeed of vertebral deforming events described by Kleerekoper et al. (5).

RESULTS

Bone density: We observed increases of vertebral density (QCT) in the range of 10-36 mg/ccm mineral equivalent (12-89% of initial values) (see Fig. 1). Increases of density could be shown with the first QCT-control after 7 months of therapy. The individual vertebrae of a single patient responded differently. There was no loss of cortical bone (SPA measurements).

Vertebral height: The index of vertebral deforming events (5) did not indicate further wedging, and excludes this as a reason of increased bone density.

Bone turn-over: The serum alkaline phosphatase increased not before the addition of calcitonin on day 15. Statistically significances was reached with day 55 (p 0,025) and day 258 (p 0,005). Serum osteocalcin levels paralleled the AP pattern tightly.

DISCUSSION

Since low doses of PTH clearly show anabolic actions on bone we combined PTH injections with calcitonin nasal spray to enhance bone mass in osteoporotic patients. This concept was proposed by Rasmussen in 1976 who used oral phosphate instead of bone active N-terminal PTH. Our study shows the combination of 1-38 hPTH and calcitonin nasal spray to be very effective in enhancing trabecular bone mass. Results are comparable to those described by Slovik et al (1) adding 1,25(OH)2 vitamin D to 1-34 hPTH injections for 12 months. Because a shift of calcium from cortical to trabecular bone might occur we exclude this by SPA measurements. Furthermore, progressive wedging can mimic therapy induced increases of bone density. We excluded this by measurements of vertebral height. From this we conclude that the dramatic improvement in bone density in our patients is only due to anabolic actions of PTH and calcitonin. Interestingly, the vertebral bodies of each individual patient responded quite different, suggesting they represent different stages in the development of osteoporosis. The increase of AP with the addition of calcitonin may show that both hormones act together at the osteoblast level but it is not clear from these results if it is direct or indirect. In future, further studies must be undertaken to optimize the rhythm and dose of hormone application. Maintaining the newly won bone mass is essential. If this is physiological bone it should be estrogen depended. In our female patients studies to demonstrate this are under way. In males androgen application should be considered, since there is growing evidence...